Study of Natural History of Sporadic Amyotrophic Lateral Sclerosis with emphasis on Cognitive Dysfunction and Objective Assessment of Upper Motor Neuron Involvement

A dissertation submitted in part fulfillment of DM Neurology (Branch I) examination of the Tamil Nadu Dr. MGR Medical University, to be held in August 2013

Department of Neurological Sciences

Christian Medical College, Vellore

CERTIFICATE

This is to certify that the dissertation entitled '*Study of Natural History of Sporadic Amyotrophic Lateral Sclerosis with emphasis on Cognitive dysfunction and objective assessment of upper motor neuron involvement*' is the bona fide original work of Dr. Varun Kataria submitted in fulfillment of the rules and regulations for the DM Neurology (Branch I) examination of the Tamil Nadu Dr. MGR Medical University, to be held in August 2013.

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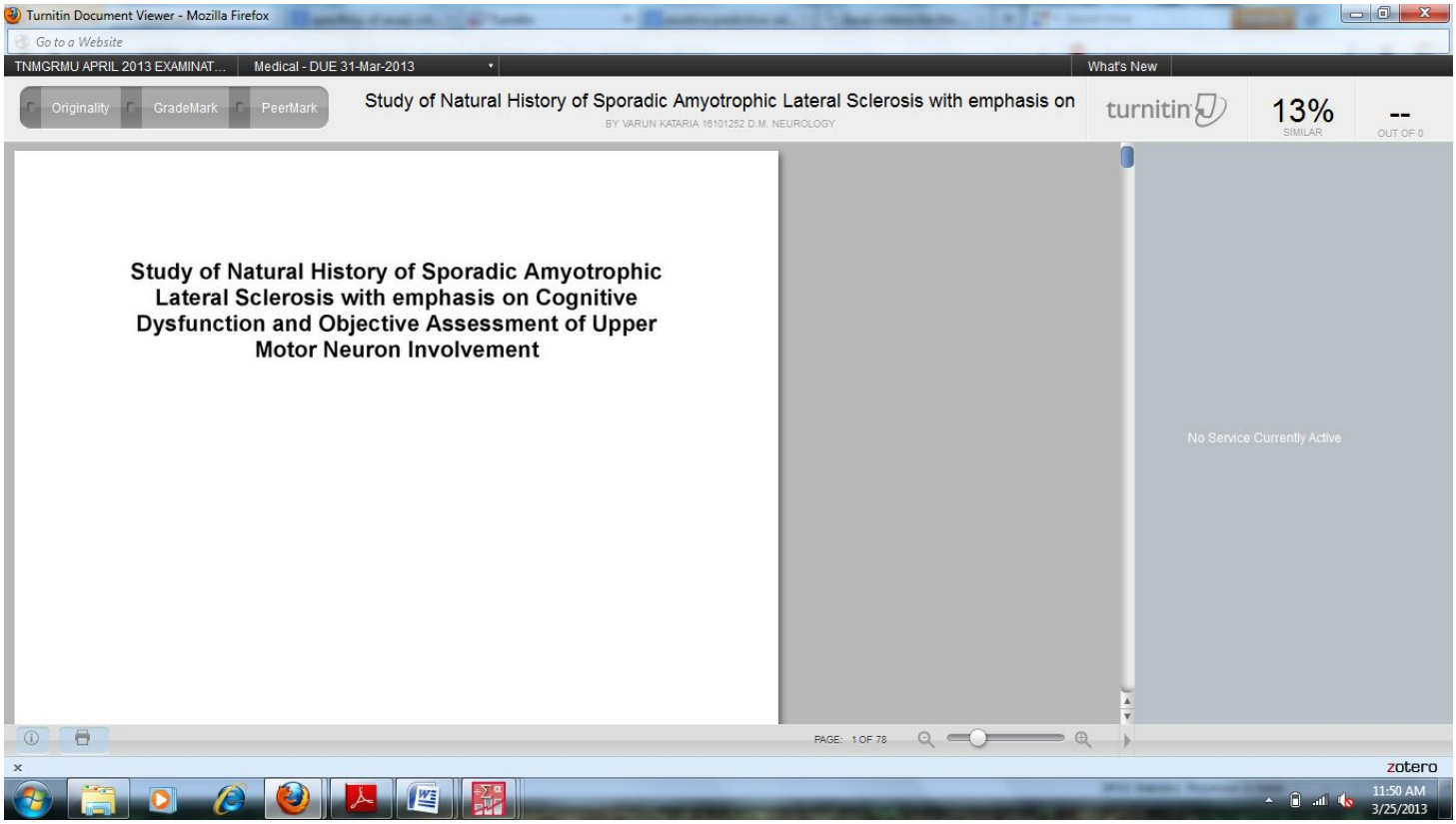

Abbreviations

1.	ALS	Amyotrophic Lateral Sclerosis
2.	PLS	Primary Lateral Sclerosis
3.	UMN	Upper Motor Neuron
4.	LMN	Lower Motor Neuron
5.	FTD	Fronto-Temporal Dementia
6.	MUNE	Motor Unit Number Estimation
7.	TMS	Transcranial Magnetic Stimulation
8.	DTI	Diffusion Tensor Imaging
9.	MD	Mean Diffusivity
10.	FA	Fractional Anisotropy
11.	ALSFRS-R	ALS functional Rating Scale
12.	CST	Corticospinal Tract
13.	PBP	Progressive Bulbar Palsy
14.	PMA	Progressive Muscular Atrophy
15.	SMA	Spinomuscular Atrophy
16.	SBMA	Spinobulbar Muscular Atrophy
17.	FALS	Familial ALS
18.	SOD	Superoxide Desmutase
19.	TDP	TAR DNA binding protein
20.	FUS	Fusion in sarcoma
21.	jALS	Juvenile ALS
22.	bvFTD	Behavior variant FTD
23.	MMSE	Mini Mental Status Examination
24.	FAB	Frontal Assessment Battery
25.	ACE-R	Addenbrooke's Cognitive Examination – Revised
26.	NIMHANS	National Institute of Mental Health and neurosciences
27.	PGIMS	Post Graduate Institute of India Memory Scale
28.	PEG	Percutaneous Endoscopic Gastrostomy
29.	PFT	Pulmonary Function Test
30.	FVC	Forced Vital Capacity
31.	VBM	Voxel Based Morphometry
32.	MTI	Magnetization Transfer Imaging
33.	MTC	Magnetization Transfer Contrast
34.	PD	Proton Density
35.	ROI	Region of Interest

LEGENDS

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INTRODUCTION

Amyotrophic lateral sclerosis is a devastating disorder with inexorable progressive course. It is the third major neurodegenerative illnesses apart from Parkinson's disease and Alzheimer's disease.

The very first report characteristic of ALS was noted by Jean- Marie Charcot (1825-1893) in 1874, and named this fatal syndrome based upon what he found. He described the clinical and pathological manifestations of "la sclérose latérale amyotrophique," a disorder of muscle wasting (amyotrophy) and sclerosis of the anterior and lateral corticospinal tracts (1).

Several other names have been given to this condition including Charcot disease, motor neuron disease, and "Lou Gehrig disease" in memory of the popular baseball player who was diagnosed with ALS in 1939 (2). Lou Gehrig was a lead baseball player in New York. His diagnosis with this disease led to his retirement in his career in 1939. He subsequently died in 1941, which brought a lot of attention to this disease.

Amyotrophic lateral sclerosis (ALS) is a disease of motor neurons. It is a progressive degeneration of the motor system at all levels - from the cortex to the anterior horn of the spinal cord (3). Thus clinical features comprise of only motor system findings. The course of the disorder is relentlessly progressive, with at least 50% of patients dying within 3 years of onset (3).

ALS can be sporadic (90%) or familial (5-10%). The familial cases usually follow Mendelian pattern of inheritance. Till date approximately 13 genes and loci of major effect have been identified (2, 3). Mutations in SOD1 account for 20% of familial ALS (6)

and 5% of apparently sporadic disease. There are only a few case reports from India (7) and the familial ALS, although very much existent, is largely an unexplored area.

ALS affects people worldwide but, an exact incidence of this disease is not yet known (8). The incidence of sporadic amyotrophic lateral sclerosis is said to be uniform throughout the world. Women have a lower incidence of disease (2.4 per 100 000 person-years) than do men (3 per 100 000 person years), although the incidence between men and women is almost the same in familial disease.

The overall lifetime risk of ALS is 1:350 for men and 1:400 for women. Peak age at onset is 47–52 years for familial disease and 58–63 years for sporadic disease. Incidence decreases rapidly after 80 years of age (7). There are no major studies from India to give information on exact prevalence and incidence of the disease in India. Reviewing the case series data and anecdotal reports (9), it can be generalized that males are more often affected than females. The disease affects people in the productive phase of their life.

The hallmark of ALS is the presence of UMN (upper motor neuron) and LMN (lower motor neuron) features. The patients can present with:

- bulbar-onset disease – seen in 25% of patients or
- limb-onset disease – seen in about 70% of cases, or
- initial trunk or respiratory involvement - 5%, subsequently spreading to involve other regions (10), (11)

Atypical ways of presentation can include cramps and fasciculations without muscle weakness, weight loss - a poor prognostic sign, emotional labiality, and frontal lobe-type cognitive dysfunction (12).

Older age of onset, early respiratory muscle involvement, and bulbar-onset variant are associated with poor prognosis and reduced survival, whereas limb-onset disease, younger age of onset, and longer time between first symptom and diagnosis are predictors of prolonged survival (13). Some ALS phenotypes tend to have a better prognosis - predominantly LMN forms like flail-limb variant ALS and progressive muscular atrophy (10, 11). Additionally, patients with primary lateral sclerosis (PLS) and predominant UMN phenotypes also progress more slowly as compared than to patients with classic ALS (10, 12). Studying these various phenotypes and distinguishing them from the typical ALS phenotype has implications not only for clinical trials of disease-modifying agents but also has a bearing on survival, prognosis, quality of life and day-to-day care of individual patients.

Most patients with ALS have mild cognitive impairment with subtle executive deficits, and 5% have a clinical subtype of fronto-temporal dementia (FTD). Many authors have since suggested that ALS and fronto-temporal dementia form a clinical and pathological spectrum. Cognitive deficits initially has a subtle appearance and more than often are overlooked in view of more prominent motor dysfunction, but with appropriate neuropsychological assessment and cognitive battery, 20–50% of patients with ALS fulfill the criteria for probable or definite FTD (16). The most common deficits involve executive function (17), either affecting language or personality. The cognitive profile mostly resembles that of behavioral-variant FTD. The clinical implications are conspicuous with

problems in judgment, impulsivity, and a general deterioration in undertaking routine daily tasks (18), Cognitive, and particularly executive dysfunction, can also adversely affect patient compliance with treatment and decision-making abilities.

One third of patients with amyotrophic lateral sclerosis report sensory symptoms and sural sensory amplitudes are also reduced a third of them. Pathologic evidence of sensory nerve pathology was present in 91% of patients who underwent sural nerve biopsy (19). The electrophysiological and pathologic findings indicate a pattern of axonal loss that predominantly affects large-caliber myelinated fibers. ALS associated with generalized sensory system abnormalities may be consistent with degeneration of motor neurons and dorsal root ganglion cells (19).

ALS was traditionally believed to spare cognitive, sensory, and affective functions, but as described above, it is now firmly established that it is not a pure motor syndrome, but more of a multisystem disorder. Most of this knowledge comes from western data. But the genetics, demography, social circumstances, education background, occupation, food habits, toxin exposure etc in Indian subpopulation bears hardly any resemblance to European or North American population. The data so obtained from literature can be extrapolated to our set-up but it can hardly be representative of our patients. In such scenario, the need of time is a longitudinal analysis of ALS patients in India.

There are various methods to assess progression of disease status in ALS. MUNE (Motor Unit Number Estimation), Axon Excitability, Transcranial Magnetic Stimulation (TMS) and clinical rating scales are few of the common once. Among all, the clinical examination and rating scales like Norris Score, Appel Scale, and ALSFRS-R – still gives

the best subjective and objective assessment over a verified duration of time. ALSFRS-R has a high reliability, internal consistency, validity, and responsiveness to change. The patients who had a low score on the scale succumb earlier than those with a higher scores, and the change in the scale also closely parallels other measures such as muscle strength, muscle mass, and brainstem abnormalities (20).

The standard of care provided is also as heterogeneous as the disease itself. Wide variety of rehabilitation and end-of-life care practices are prevalent in India. The other unique fact considering Indian scenario is the use of Indigenous and native medications, some of which contains toxic substances like heavy metals contributing to rapid progression of the disease. Also, these potentially toxic substances could also add on to the on-going pathology leading to clinical findings of Myokymia which have not been well characterized in literature. These also have an effect on cognition (21).

The cognitive involvement can be studied and objectively documented by multidisciplinary higher mental function tests. LMN degeneration is also well characterized by bed-side motor system examination as well as electromyography/nerve conduction tests. But the challenge is to objectively demonstrate and quantify UMN pathology which often starts in the primary motor and premotor cortex. It is often difficult to decide whether the UMN is involved. Both neurophysiological and neuroimaging techniques have been used to evaluate UMN pathology.

Diffusion tensor imaging (DTI) is a relatively new method in structural neuroimaging. It estimates the orientation of fibers in white matter on the basis of the diffusion characteristics of water. Diffusivity is generally higher in directions along fiber tracts than

perpendicular to them (22). The directionality of diffusion can be quantified by the fractional anisotropy index. Fractional anisotropy (FA) values range from 0 (no directional dependence of diffusion coefficients) to 1 (diffusion along a single direction). Changes in tissue structure (in this case degeneration of the corticospinal fibers) can lead to a modification of the degree of directionality, which can be detected by diffusion tensor MRI. Therefore, in degenerated white matter tracts of patients with ALS one would expect to find changes in the anisotropy of diffusion in comparison with healthy subjects (23).

The heterogeneity in presentations of ALS (24) are thus crucial to the understanding and development of measures of disease progression (25). The identification and conceptualization of specific phenotypes has often, indirect but vital implications for patients particularly, with regards to prognosis and survival. In a resource crunch country like ours, it is even more important to know exactly the pattern of onset, spread and progression of the disease so that management options can be individualized. It will also aid in optimal utilization of resources with higher yield and economic precision. Thus a proper study of natural history of ALS in Indian subpopulation is must along with an in-depth insight into the multisystem nature of the disease. This was one of the crucial factors that motivated us to plan this study.

AIM AND OBJECTIVES

Aim:

To study the natural history, multisystem nature and spectrum of cognitive dysfunction in sporadic Amyotrophic Lateral Sclerosis along with objective assessment of Upper Motor Neuron (UMN) involvement utilizing diffusion tensor MRI (DTI).

Objectives:

A. Retrospective Part:

1. To study and document the pattern of onset, spread and rate of progression of Sporadic ALS.
2. To study the spectrum of motor and extra-motor manifestations of Sporadic ALS.
3. To evaluate and analyze the outcome, factors affecting prognosis, effect of therapeutic intervention.

B. Prospective Part:

4. To assess spectrum of cognitive & behavioral dysfunction in sporadic adult onset ALS utilizing Cognitive Batteries and rating scales – PGI Memory Scale (P.G.I.M.S.), NIMHANS Battery, Frontal Assessment Battery (FAB), and Addenbrooke's Cognitive Examination (ACE-R).
5. To compare the DTI indices of patients with ALS with that of normative data.
6. To correlate DTI indices and cognitive dysfunction scores.
7. To correlate DTI indices and disease severity in amyotrophic lateral sclerosis using functional rating scale – revised (ALSFRS - R)

REVIEW OF LITERATURE

“A-myo-trophy” is the term derived from Greek meaning “no-muscle-nourishment.”

“Lateral” refers to the location of the corticospinal tract (upper motor neuron) in the spinal cord. Hardening or scarring of the nerves and tracts due to degeneration is referred to as “sclerosis”.

Amyotrophic lateral sclerosis is a rare neurodegenerative disease which causes loss of upper and lower motor neurons. The motor neurons are lost from the spinal cord, brain stem and from the cerebral cortex. This then results in progressive wasting and paralysis of voluntary muscles. It is the most progressive form of motor neuron disease and causes respiratory insufficiency and death within three to five years of illness (26).

Types of Motor Neuron Diseases:

MND is phenotypically heterogeneous, encompassing progressive muscular atrophy (a purely lower motor neuron disorder), primary lateral sclerosis (an exclusively upper motor neuron disorder), ALS (which combines both upper and lower motor neuron features), as well as progressive bulbar palsy, a segmentally predominant form of the disease.

Classical motor neuron disease seen in India is similar to the western population; however the onset is earlier by about a decade and patients below the age group of 30 years is quite high (27, 28).

Two subtypes have been described in India.

1. Single limb involvement also called as "juvenile muscular atrophy of upper extremity", monomelic amyotrophy", "wasted leg syndrome" and "benign focal amyotrophy"

2. Madras pattern of motor neuron disease which was first described by Meenakshisundaram & Jagannathan K from South India in 1970.

The madras pattern of motor neuron disease has an earlier onset (between the ages of 10 to 30 years) with predominantly male involvement. It usually has a benign course and absence of family history. There is usually gradual asymmetric onset of involvement of the limbs with wasting. Involvement of the lower cranial nerve nuclei was described. Sensorineural hearing loss has been described has the hallmark of Madras Motor Neuron Disease (MMND). The other features include involvement of the lower cranial nerves – seventh, ninth and twelfth with involvement of the facial and bulbar muscles.
There is a variant of MMND called as the Madras Motor Neuron Disease Variant (MMNDV) in which patients have optic atrophy. A few cases of familial MMND (FMMND) have also been described with mode of inheritance being autosomal recessive (29,30, 31,32).

Epidemiologically it can be classified into sporadic (90%) and familial forms (10%). In the familial group mutations in SOD1 (encodes for superoxide dismutase-1: SOD1) gene are found in one fifth of familial ALS cases, mutations in the RNA-processing genes TDP-43 (TAR DNA Binding protein), and FUS (encodes fusion in sarcoma) are also found in one tenth of the cases (10, 9). Between 5% and 10% of ALS is familial - familial ALS (FALS) (33).

When the onset of the illness is less than 25 years of age the term Juvenile onset ALS (jALS) is used. Most of these cases are autosomal recessive. Gene mutations may cause autosomal dominant inheritance.

The World Federation of Neurology Research Group on Neuromuscular Disorders has classified ALS as a disorder of motor neurons of undetermined etiology, and several variants are known (34). It is essential to know that ALS is a progressive dynamic disorder. Some cases present with the classic combination of UMN and LMN signs, but others may have UMN onset, LMN onset, bulbar onset, or dyspnea at onset and only later develop signs of involvement of the other parts of the motor system. The mean duration from onset to death is about 3 years, but around 1 in 5 patients survive to 5 years, and 1 in 10 patients survive to 10 years (35).

Causes

There are no specific environmental, physical, or occupational factors that can be associated with absolute certainty to an increased risk of ALS. Possible factors include chronic exposure to electromagnetic fields, high physical (sports) activity, high intake of glutamate in diet, environmental toxins, and a history of service in the Persian Gulf War.(36) Smoking is an independent risk factor for sporadic ALS, with a higher risk for those who have smoked for many years (37),(38). Several environmental trace elements like Selenium, iron, aluminum, copper, manganese, zinc, cadmium, and lead have been postulated as causative agents for ALS, but there is no conclusive evidence that any one of these plays a vital part in ALS pathogenesis (39).

A recent study in Indian population showed that rural livings, smoking, insecticides, and pesticides exposures, electrical injury are “associated factors” in development amyotrophic lateral sclerosis (9).

Clinical Features:

The hallmarks of ALS pathology are the degeneration and loss of motor neurons. Both UMN and LMN cell loss occurs. UMN cell loss occurs in the motor cortex (Betz cells from Brodmann area 4) and axonal loss in corticospinal tracts (CST). LMN loss occurs in the brainstem and spinal cord. Extramotor pathology includes involvement of the fronto-temporal cortex, thalamus, hippocampus, dorsal columns, spinocerebellar tracts, and substantia nigra (40).

The typical clinical picture in ALS is that of a patient with a progressive motor deterioration manifesting with both UMN and LMN symptoms and signs. The classic pattern is that the muscle weakness in ALS begins in a focal area, first spreading to contiguous muscles in the same region before involvement of another region. But not all patients present with this classical pattern. Upper limb Onset is more common than the lower extremities (classic, spinal ALS), but in approximately 25% of patients, weakness begins in bulbar-innervated muscles (bulbar-onset ALS). On rare occasions (1% or 2% of patients, more often male), the weakness starts in the respiratory muscles (dyspnea or respiratory-onset) (41). Various presentations can be there including pseudopolyneuritic or flail leg presentation (42), monomelic presentation(27), 43), Mills hemiplegic variant, flail arm or flail person in the barrel variant.(44). The flail arm variant is also is known as the brachial amyotrophic diplegia or the Vulpian-Bernhardt syndrome. In this condition

there is weakness involving predominantly the upper limbs. To understand these different variants is very important because the natural history, prognosis and survival are different in each of these. And based only on these accurate facts, one can plan management and rehabilitation tailored to each phenotype, and ultimately to each individual.

As the disease advances, motor function is progressively impaired, and activities of daily living (e.g., self-hygiene, bathing, dressing, toileting, and walking, feeding, and verbal communication) become difficult. Accordingly, a patient's quality of life progressively deteriorates.(45)

As dysphagia worsens, muscle weakness is accelerated by reduced caloric intake (46). Aspiration of liquids, secretions, and food becomes a risk. Weight loss is often rapidly progressive; this is not simply due to poor caloric intake but represents ALS cachexia (47). Sleep disturbances in the form of increased awakenings from hypopnea and hypoxia are common in ALS and contribute to daytime sleepiness, morning headaches, and fatigue. As respiratory difficulty worsens, orthopnea sets in because of worsening diaphragmatic weakness and thus compensate by using multiple pillows (48).

Extra-motor Features

Cognitive impairment is present in many patients with ALS, but on a spectrum from apparently normal to a frank FTD (Fronto-temporal Dementia)(49). These observations support the idea that ALS is not a pure disorder of motor neurons, but rather a disorder that mainly affects motor neurons, with the potential to involve other nonmotor systems (40). One needs to be cautious while assessing patients with apparently normal

cognition because the deficits may be subtle requiring specific assessments of personality, behavior, verbal fluency, visual attention, and verbal reasoning (50). Dysarthria may hide language disturbances (especially anomia). With appropriate tests, cognitive deficits may be diagnosed in about 50% of patients with ALS, but the full (Neary) criteria for diagnosis of FTD are met only in about 20% of cases (51, 52). In India, the social circumstances are such that many of these cognitive features are labeled as part of aging or of premorbid personality. It's very difficult to find families coming up with symptoms of cognitive involvement when they bring their family member for evaluation of ALS. There is a paucity of Indian literature on cognitive profile of ALS patients in India.

It is extremely rare to see are extrapyramidal dysfunction, abnormal sphincter control, eye movement abnormalities, and autonomic disturbances. Approximately 5% of patients with ALS show signs of extrapyramidal dysfunction, usually retropulsions during attempted ambulation (44). Autonomic dysregulation is part of degenerative process in ALS. There's considerable decline in sweat secretion (about 20- 40%) over a six month period. Overall, the pattern seen in few of the cases is an abnormal sympathetic activity with hyperhidrosis in early ALS and as the disease progresses, a reduction in sweat production. (53) One of many phenotypes of SOD1-associated ALS has showed involvement of the autonomic nuclei in the medulla and spinal cord by a neuropathologic study. (54)

The ongoing research in the field and thorough epidemiological studies, these abnormalities are being documented in more number of patients. There have been patients who are kept on mechanical ventilation to prolong life and eye movement abnormalities have been documented.

There are anecdotal reports on sensory involvement in patients with ALS, with clinical, electrophysiologic, and pathologic evidence of sensory nerve pathology (19). This suggests that the typical ALS phenotype is perhaps broader than previously recognized and includes abnormalities of peripheral sensory nerves. Their presence emphasizes the point that the motor neuron diseases, although named after the predominant system affected, are characterized by pathology that extends beyond involvement of upper and lower motor neuronal systems. This recognition may have implications for the way in which we conceptualize these diseases and impact our efforts to investigate and understand their basic biology and pathophysiology.

Natural History - Onset & Progression

A linear decline in motor functions is observed once the motor weakness is evident. The pattern of disease spread was thought to be predictable. When onset is in one arm, spread is often first to the contralateral side, then the ipsilateral leg, the contralateral leg, and finally the bulbar region. Onset in the leg often follows the same pattern, with final involvement of the bulbar region. Bulbar-onset ALS tends to spread to the hands first, with spread to thoracic myotomes, and then the legs. Overall, the pattern suggests that rostral-caudal involvement is faster than caudal-rostral spread. During the course of the

disease, transitory improvement, plateaus, or sudden worsening can occur, but spontaneous improvement, is exceedingly rare.

The onset and spreading pattern was looked in detail by F. Kimura et al (55). They studied 150 patients of ALS. Onset was in the upper limbs in 33%, lower limbs in 35% and bulbar in 21%. Overall median survival time was 32 months and mean duration from FS-FE (first symptom to first examination) was 14.3 months. Survival was significantly shorter with bulbar onset (26 months) than with upper limb onset (33 months) or lower limb onset (32 months). A female predominance with older disease onset was seen in patients with bulbar onset. The Fist Symptom-Second Symptom (FS-SS) time interval is an important predictor of survival. The faster the subsequent region/myotome gets affected, the shorter is the survival. But survival was not linked to any particular combination of FS-SS, but only to the interval of FS-SS. Early manifestation of bulbar symptoms within 1 year was also an important predictor of shorter survival. The spread to the contiguous or skip area depends on the onset. When the illness starts with the lower limbs, 83% of cases were followed by upper limb symptoms, 3% by respiratory symptoms and 14% by bulbar symptoms. When the course began with bulbar symptoms, 71% of cases were followed by upper limb symptoms, 29% by lower limb symptoms and 0% by respiratory symptoms. When the course began with upper limb symptoms, 64% of cases were caudally followed by lower limb symptoms, 5% by respiratory symptoms and 32% were rostrally followed by bulbar symptoms. No patient with bulbar onset skipped directly to respiratory symptoms without upper limb involvement. This knowledge about the pattern of onset and the anatomical direction of spread may provide valuable prognostic insights.

Poor Prognostic factors

The proven poor prognostic factors in ALS are older age at onset and bulbar-onset pattern (57). Other important poor prognostic factors include shorter interval between onset and clinical diagnosis (a more aggressive onset), rapid progression rate, low body mass index, FTD-ALS presentation, dyspnea at onset, and rapid rate of decline in pulmonary function.(58)(59) Those who have low-amplitude CMAPs in the setting of normal sensory potentials (the “generalized low motor-normal sensory pattern”) as revealed by nerve conduction studies appear to have a poor prognosis.

Investigations: EMG

Investigations are necessary to exclude other possibilities although the diagnosis of clinically definite ALS can sometimes be established on the history and clinical examination alone. The electrodiagnostic investigation is an essential tool in the evaluation of ALS and its variants. It serves as an extension to the clinical examination and is particularly useful in determining the presence or extent of LMN disease. But none of the EDX findings are specific for ALS, although they can strongly support the diagnosis. Disease monitoring can be done by repeated investigations at intervals. Sensory nerve conduction studies are characteristically normal (60).

In classical cases, nerve conduction studies provide only a little supportive evidence for the diagnosis. The sensory nerve action potentials (SNAPs) are normal and there is reduction in compound muscle action potentials (CAMPs) amplitude, reflective of the motor axonal loss from the death of the anterior horn cells. The motor nerve conduction velocities and distal latencies can be delayed due to the loss of motor axons. Sensory

nerve conduction velocities and distal latencies should be normal. There should be no evidence of motor conduction block but exceptions are always present (61, 62).

The EMG examination characteristically reveals a combination of acute (positive sharp waves and fibrillation potentials) and chronic (reduced neurogenic firing pattern with evidence of increased amplitude and duration, polyphasic motor unit potentials) changes in a distribution that does not concur with any single root or peripheral nerve distribution. Fasciculation potentials are common and typically of complex morphology; their absence should push us to investigate for another disease (60). The recent Awaji-shima criteria for the neurophysiological diagnosis of suspected ALS stresses the importance of fasciculation potentials: the presence of fasciculations potentials is enough evidence of acute denervation in the similar way that one considers fibrillation potentials and positive sharp waves. (63)

As the disease progresses and the anterior horn cells are lost, the more typical changes in motor unit potentials that are associated with ALS will be seen, including long duration, increased complexity, and reduced recruitment. Motor unit instability remains a prominent feature, and motor unit variability remains highly visible and audible throughout the course of ALS.

Neuroimaging studies:

UMN assessment has been made possible with advent of Functional imaging studies with blood oxygenation level–dependent (BOLD) functional MRI and magnetoencephalography which may reveal abnormal activity in motor and non-motor areas in ALS. Similarly, the role of transcranial magnetic stimulation (TMS), whether

used alone or in combination with diffusion tensor MRI (DTI), in the evaluation of the UMN system is undeniable.

The LMN involvement is objectively assessed and very well documented by detailed NCV/EMG studies that are generally available at most centers. Decrease MUP firing rate may be the only evidence for UMN involvement in ALS that NCV/EMG can provide. But the challenge is to objectively demonstrate and quantify UMN involvement (64). Upper motor neuron (UMN) pathology often starts in the primary motor and premotor cortex, with secondary degeneration of motor fibers and gliosis along the corticospinal tract. It is often difficult to decide whether the UMN is involved. Both neurophysiological and neuroimaging techniques have been used to evaluate UMN pathology. The most important role for neuroimaging studies in ALS is to exclude structural, inflammatory, or infiltrative disorders that may mimic this disease, and therefore all patients should undergo appropriate imaging of brain and spinal cord to rule out any lesions in the brain parenchyma, lesions at the skull base, cervical myelopathy and thoracolumbar sacral radiculopathy.

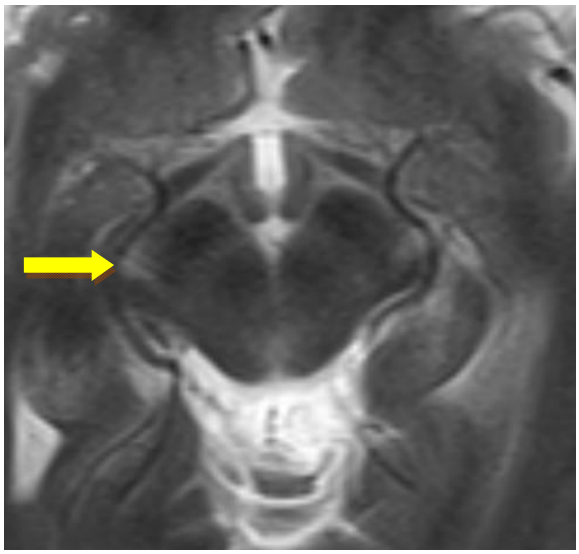
The diagnosis of ALS as seen previously needs both UMN and LMN signs. LMN signs can be diagnosed using electromyography there is no accepted marker for UMN signs. Clinical proof of UMN signs especially in early disease is difficult. (65) (66) (67)

Conventional MRI:

Neuroimaging signs that may support the diagnosis of ALS but are not specific for ALS are hyperintensity extending along the corticospinal tracts, motor cortex showing hypointensity and cerebral atrophy. (65) (66) (67)

Hyperintensity along the corticospinal tracts:

In patients with ALS conventional MRI (using T2, PD and FLAIR sequences) hyperintensity is seen along the corticospinal tract. The corticospinal tract changes are usually best appreciated in the coronal views. They are seen as bilaterally increased signal which extend along the tract from the centrum semiovale to the brain stem. The frequency of this finding varies in different studies and ranges from 15 to 76 percent. Using a combination of T2, PD and FLAIR showed a sensitivity of 62 percent.



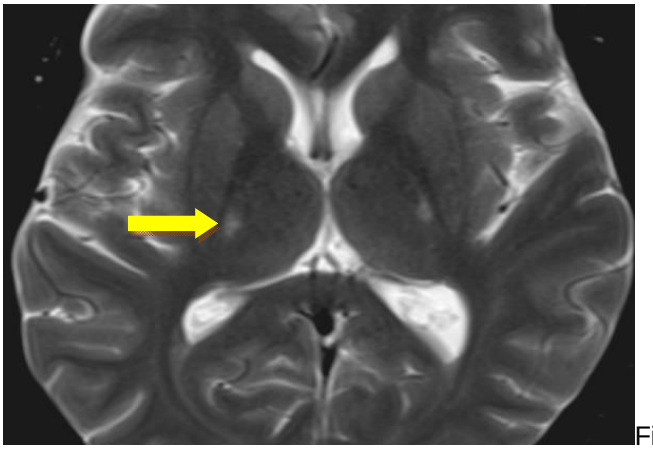


Fig 2

Fig 3

T2 W axial: Hyperintensity extending along the corticospinal tract in the cerebral peduncles and along the corticospinal tract in the posterior limb of internal capsule.

As compared to the routine T2 sequences the proton density images has been reported to have a greater specificity. Cheung et al reported a specificity of 100% and a sensitivity of 41–60% using PD images which showed hyperintensity along the corticospinal tract (68).

It has been reported that the hyperintensity along the corticospinal tracts can be seen in other diseases as well like Krabbe disease, adrenomyeloneuropathy and X-linked Charcot-Marie Tooth neuropathies. It has also been described in normal individuals as well (69).

Hypointensity in the motor cortex:

T2 weighted images have shown some hypointensity in the motor cortex in a few percent of cases. Hypointensity may be due to iron deposition which causes T2 shortening, gliosis or infiltration by macrophages. However these changes are neither specific nor sensitive for ALS pathology. It can be seen in healthy population as well as those with other degenerative diseases. Cortical low signal intensity is seen in the precentral gyrus on T2 or FLAIR called as the “motor dark line” or “hypointense rim”. These have been described as UMN involvement in advanced disease. (65, 66, 67, 69, 68)

Cervical cord:

Anterolateral columns of the spinal cord also may shows hyperintensity on T1WI in patients with ALS. Anterolateral column hyperintensity has been noted in the intracranial portion also in patients who have predominantly UMN signs. (66)

Diffusion tensor imaging: (DTI)

Diffusion tensor imaging can be used to diagnose upper motor neuron involvement in patients with ALS. The changes within the tissue alter the DTI indices – FA and MD values. FA values will be decreased and MD will be increased with loss of normal neuronal structure and function. Damage and loss of motor neurons in the primary motor cortex along with axonal degeneration of the corticospinal tract, glial cell proliferation, expansion of the extracellular matrix contribute to the changes observed on DTI (70). Many studies have shown significant correlations between the DTI indices along the corticospinal tract in patients with ALS. (65, 22, 71, 72, 73, 74)

The corticospinal tract is the most commonly studied region and a reduction in FA values within this have been reported in may studies. (74) The reduction in FA value as mentioned earlier is due to loss of normal neuronal integrity. Mean diffusivity values have shown to be increased in some studies (71, 72, 75) along the corticospinal tract ; however few studies have revealed no changes in the MD values (76).

Sage et al. (75) showed that FA values were reduced at nearly all the levels within the corticospinal tract with was most significant at the level of the posterior limb of the internal capsule.

Few studies have demonstrated significant correlation with the severity and duration of the disease (71, 74, 76). However these findings are not consistently seen in all the studies. Toosy et al. (72) have shown no correlation between the markers of disability and diffusion tensor indices.

DTI indices are routinely calculated from a voxel based analysis. Another recently developed technique known as the tract-based spatial statistics (TBSS) combines voxel based and tract based analysis is being recently used for the same. (65)

There are many studies that also reveal that abnormalities of the DTI indices are not only seen in the corticospinal tract but in extramotor regions as well. These include the corpus callosum, white matter in the frontal and parietal regions, hippocampus and insula.(69, 70, 75, 77, 78). Agosta et al reported that the uncinate fasciculus has shown increased diffusivity values at the in patients who had ALS. This suggested that the behavioral abnormalities in ALS patients may be due to involvement of the uncinate fasciculus (23). Meta-analysis done by Li J et al comparing 145 healthy controls and 143 ALS patients showed that significant reductions of the FA values in the bilateral frontal white matter/cingulate gyrus and the posterior limb of bilateral internal capsule (79).

When compared with healthy population there was a significantly lower value of FA in the cervical cord. This was also found to be correlated with the functional rating scales (77).

Corpus callosum has been shown to be involved in patients with ALS using DTI indices. The FA changes were most pronounced in the middle and posterior parts which connect

to the motor and premotor cortex. The involvement of the corpus callosum may be an earlier feature of the disease.

These findings in the corpus callosum are not specific and may be seen in other conditions like hereditary spastic paraparesis. (70, 77)

Patients with bulbar onset of ALS have shown more markedly reduced FA values. In patients with progressive muscular atrophy there were reduced FA values noted in the premotor cortex and corticospinal tracts. (70, 80) Thus this suggests that DTI may be good marker for clinically silent UMN involvement. In a study done by Ciccarelli et al shows those patients with primary lateral sclerosis had reduced FA values in the white matter adjacent the premotor cortex as compared with patients with ALS who had FA values reduced in the frontal region (81).

Foerster et al. in 2012 compiled data and a meta-analysis was done on FA values in studies that compared healthy controls and ALS patients. They have reported that the use of DTI has only a modest role in making the diagnosis of ALS (82).

There are few studies that have evaluated the role of DTI in the spinal cord in patients with ALS. In a study done by Valsasina P et al patients with ALS showed a lower FA values within the cord when compared with healthy controls; however there was no change in the MD values (83). They also found a significant correlation of the ALSFRS with FA values in the cord. Another study reported by Nair et al. also showed that the FA values were lower in the cord in patients with ALS and radial diffusivity was higher when compared with healthy controls. Radial diffusivity also correlated with the forced vital capacity and the functional rating scale in these patients (22). The degeneration in the

corticospinal fibers can lead to a modification of the degree of directionality, which can be detected by diffusion tensor MRI. Therefore, in degenerated white matter tracts of patients with ALS one would expect to find changes in the anisotropy of diffusion in comparison with healthy subjects. The fractional anisotropy correlates with UMN involvement in ALS patients.

Studies have shown relation of DTI indices with cognitive involvement in ALS (84). The severity of apathy and behavioral changes in early ALS has been proven to correlate with atrophy in the prefrontal cortex, especially in the orbitofrontal and dorsolateral prefrontal cortices in Voxel Based Morphometry (VBM), and in the right frontal gyrus in DTI. The combined VBM and DTI techniques have revealed extra-corticospinal tract neuronal degeneration mainly in the frontotemporal lobe of ALS patients. In particular, follow-up examinations in these patients have showed that whole-brain DTI changes occurred predominantly in the regions of brain atrophy. These objective analyses were comparable with drop in clinical scores in frontal lobe tests when serially monitored (85, 86).

Differential diagnosis includes disorders of motor neurons (eg, SMA), motor neuropathies – multifocal motor neuropathy with conduction block, CIDP, lead poisoning, Neuromuscular disorders, lesions in the central nervous system (Lyme's disease, HTLV, Syringomyelia), myopathies (IBM) and various endocrine causes (10).

The clinical findings pertaining to both upper motor neuron and lower motor neuron dysfunction which is not explained by any other disease process along with history suggestive of a neurodegenerative disorder, is suggestive of ALS.

The diagnosis of amyotrophic lateral sclerosis is mainly established through history and clinical examination alone. But since the diagnosis has a serious impact on the patient and family ancillary investigations are done to exclude other differential diagnosis.

DIAGNOSIS*

In May 1990, at El Escorial, Spain, the World Federation of Neurology established diagnostic criteria for ALS. These criteria include clinical, electrodiagnostic, and pathological components. The clinical criteria divide candidates into those with definite, probable, lab-supported probable, possible, and FALS based on a careful history and examination of four regions of the neuraxis: bulbar, cervical, thoracic, and lumbosacral (87).

A patient is referred to as having “definite ALS” if there is clinical evidence of both UMN and LMN signs in three or more regions. “Probable ALS” is UMN and LMN signs in two regions. “Possible ALS” implies that a patient either has UMN and LMN signs in one region only or has UMN signs alone in two regions. In addition, “possible ALS” may be applied to those with LMN signs in two regions as long as these are detected rostrally to the UMN signs. “Probable ALS-laboratory supported” refers to those patients who have clinical evidence of possible ALS but also have EDX evidence of more widespread LMN involvement. Follow-up examinations may be helpful in assessing patients with ALS, as disease progression may move a patient up a category, clarifying the diagnosis.

Signs of denervation in EMG, however, were regarded as equivalent to clinical signs of the lower motor neuron and it was suggested to delete the category “laboratory supported probable ALS” and to use only the category “probable ALS”. The essential

difference between the EEC and the Awaji Criteria is that the latter regard fasciculation potentials in muscles with chronic neurogenic EMG-changes in a clinical context fitting with ALS as sign of “active denervation” even in the absence of fibrillation potentials and positive waves. This improves the sensitivity of EMG studies considerably without increasing the rate of false positive diagnoses as has recently been demonstrated (88),(89), (90)

Using both sets of criteria together, namely Revised El Escorial and Awaji Criteria; Carvalho and Swash demonstrated an increased sensitivity in the diagnosis of bulbar-onset ALS from 38% with revised El Escorial alone to 87% when both sets of criteria were used. Another group achieved a specificity of over 95% when using both sets of criteria together (89, 91).

Table-1. **EMG features of the revised El Escorial criteria**

Level of Certainty Regions Involved	**Level of Certainty Regions Involved**
Possible ALS	1 region
Probable ALS	2 regions
Probable ALS – Laboratory Supported	1 region clinically, 1 region electrodiagnostically
Definite ALS	3 or 4 regions

*Flowchart for diagnostic criteria and algorithm given in **Appendix – 9**

The utility of DTI is that the anisotropy indices are rotationally invariant, that is, they are insensitive to the orientation of: the subject in the scanner, the diffusion gradients, and the laboratory coordinate system. As such, the quantitative anisotropy values obtained from different patients, at different times, and from different MRI systems should be directly comparable provided the same acquisition scheme is always used. Therefore, diffusion anisotropy measures are suited to monitoring the progression of UMN

involvement over time, which is helpful in evaluating the efficacy of novel pharmaceutical compounds (76). This implies that a single cross-sectional study may not be that informative as would a longitudinal study with serial follow up of patients.

There is usually a delay in reaching the diagnosis due to insidious onset of the disease. Mean time of diagnosis from the onset is about a year. Diagnostic delay leads to delay in starting treatment and symptomatic therapy. The ascertainment of diagnosis of ALS and breaking the news to the patient and family members is very important and sensitive matter. Clinicians need to rule out conditions that may mimic ALS (92).

ALS – functional rating scale:

Activities of daily living (ADL) can be assessed by using the clinical rating scales. Earlier Norris scale and the ALS severity scale were used. The two most commonly used ones are the Appel ALS rating and the ALS Functional Rating Scale (ALSFRS).

The total Appel ALS score in a healthy individual is 30 and 164 in those patients who are maximally impaired. Survival of the patient can be predicted by the rate of change in the Appel ALS Rating Scale.(26, 93)

ALS functional rating scale: The ALS Functional Rating Scale (ALSFRS) is a rating scale used to monitor disease progression and disability in patients with ALS. It is a relatively simple scale which can be done quickly. It assesses the patient's capacities and varying levels of independence in the daily activities. It assesses bulbar and respiratory functions along with swallowing, speech, salivation, upper extremity functions (handwriting, cutting food and dressing), lower extremity functions (walking and climbing), and dressing

hygiene and ability to turn in bed. It can be administered by any health care worker. There are five choices in each choice has a score from 0 to 4. The total score can range from 40 (normal function) to 0 (unable to attempt the task). The ALS score correlated well with the quality of life and also predicted survival. Since there was disproportionate weighting to limb and bulbar functions, as compared to respiratory dysfunction in the original ALSFRS a new revised ALSFRS-R is used. ALSFRS-R has additional assessments of orthopnea, dyspnea and the need for ventilatory support. The revised ALSFRS- R has a minimum score of 0 and a maximum of 48. It correlates significantly with the quality of life (93). ALSFRS – R is enclosed in Appendix 3.

MATERIALS AND METHODS

Study design:

There are two parts in this study:

1. **Retrospective Cohort Analysis** – Data of patient with the diagnosis of Sporadic Amyotrophic Lateral Sclerosis (ALS) during the last 10 years (2002-Oct 2012) was analyzed. The following were assessed:

- Pattern of onset (upper limb onset, lower limb onset, bulbar onset),
- Presenting features (weakness, wasting, fasciculations),
- Progression & Outcomes (time to respiratory dysfunction, loss of ambulation, wheel chair bound)
- Atypical features (sensory abnormality, Extra-motor abnormalities)
- Investigations (electrophysiology and neuroimaging)

Data source – OP / IP records, telephonic interview, Last medical report

2. **Prospective Analysis** – The upper motor neuron involvement was analyzed by:

- Assessment of cognition (ACE-R, PGIMS, FAB, NIMHANS Battery)
- Structural integrity of corticospinal tracts by Fractional Anisotropy (FA) by Diffusion Tensor Imaging (DTI).

This was a cross sectional study with a prospective patient enrolment. There were two patient groups in this study namely, normative data group and ALS group.

Study period:

The study period was from September 2012 to February 2013.

Ethical clearance: Ethical clearance was obtained from the Institutional review board (ref no: IRB min number 8057).

Study setting:

The study patients were those who attended the Neurology outpatient clinic and patients who were admitted under the Department of Neurology at Christian Medical College & Hospital, Vellore

Inclusion criteria:

1. Normative data group: Patients aged 35-65 years who underwent MRI brain for any reason (E.g. head ache evaluation) and in whom the MRI showed no obvious abnormality (as reported by the radiologist) were recruited for generating normative data. In all these patients there was no history suggestive of motor system involvement or amyotrophic lateral sclerosis and no abnormal neurological findings clinically.

3. Amyotrophic lateral sclerosis group: Patients of any age above 25 years who were diagnosed to have sporadic ALS using Revised El Escorial – Awaji Algorithm.

Inclusion Criteria for Retrospective part of the study:

Patients of Sporadic ALS evaluated (OP and IP) in CMC hospital in last 10 years (Diagnostic criteria – Revised El-Escorial criteria & Awaji-shima criteria)

Exclusion criteria for Retrospective Part of the study:

Other Motor Neuron Diseases like

Primary Lateral Sclerosis

Flail arm and limb phenotype (Pure LMN variants)

Motor neuropathy with conduction blocks

Primary Muscular Atrophy

Patients coming for an evaluation and undergoing investigations as part of standard of care (EMG/NCV, MRI Brain & cervical Spine and other relevant tests) were the potential subjects. After applying Revised El Escorial criteria, they were labeled as Sporadic ALS. Functional scale (ALSFRS-R scale) was applied and correlated with above findings. Each case was compared with age-matched and sex-matched healthy control. The control group was taken from general population as stated above. The scores of cognitive battery and FA were taken in cases as well as in controls and appropriate statistical tests were applied. The pattern of onset, spread and progression in prospective group was analyzed in detail.

Outcomes – Mortality

Exposures – Nil

Confounders – Socioeconomic background, Education status, Family support, systemic co-morbidities

Diagnostic Criteria – ***Appendix 9, Table 4***

Informed consent: Informed consent was taken from all patients being enrolled in the study. The sample copy of consent form is given in ***Appendix 1, 2.***

MR data acquisition:

Examinations were performed with 1.5-T MR imaging Philips (Achieva, Philips medical systems, Koninklijke Philips electronics, Netherlands) machine. None of the patients needed sedation or anesthesia for the MRI.

DTI indices:

The movement of water molecules is determined by the eigenvectors and eigenvalues (λ 1, λ2, λ3). Eigenvalues represent the magnitude of water movement along the direction of the corresponding eigenvectors.

Fractional anisotropy was calculated by the formula:

$$\frac{\sqrt{3/2} \times \sqrt{(\lambda 1 - MD)^2 + (\lambda 2 - MD)^2 + (\lambda 3 - MD)^2}}{\sqrt{\lambda 1^2 + \lambda 2^2 + \lambda 3^2}}$$

The FA and the eigenvalues were provided by the soft ware available in the MRI console.

Placement of ROI in normative data group:

Levels at which the regions of interest (ROI) were placed include subcortical white matter just below the motor cortex (at the point at which the corticospinal tract is seen close to the gray matter), posterior limb of internal capsule (PLIC), anterior and posterior parts of the deep periventricular white matter, in the frontal lobe white matter bilaterally, cerebral peduncles in midbrain, and the pyramids in the medulla. The ROIs were also placed in the genu and splenium of the corpus callosum and in an area of normal white matter with in the right Centrum semiovale.

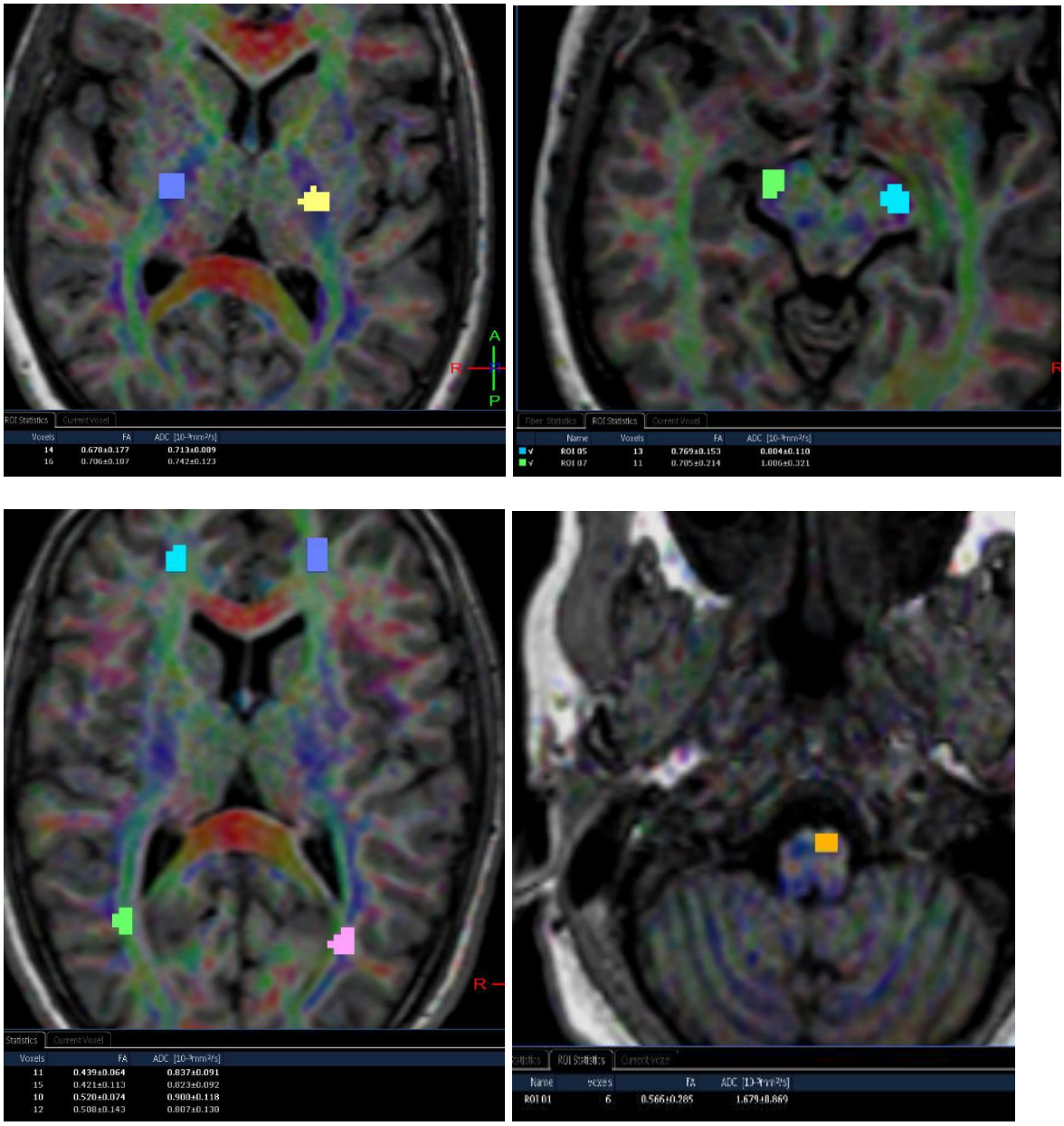


Fig 4 - ROI were placed at the following locations: Posterior limb of internal capsule [A]; cerebral peduncles [B]; Deep white matter at the periventricular region [C]; Pyramids [D]

Placement of ROI in amyotrophic lateral sclerosis:

Regions of interest were placed in the subcortical white matter just below the motor cortex (at the point at which the corticospinal tract is seen close to the gray matter), posterior limb of internal capsule, cerebral peduncles and pyramids bilaterally.

Sample size:

The prevalence of Amyotrophic Lateral Sclerosis is around 3 -8 /100,000. Owing to the rarity of the disease the sample size was taken to be thirty five.

In our tertiary care hospital approximately 30000 patients are being seen in the outpatient clinic in Neurology in one year. On an average there are around three to five patients per week with suspected amyotrophic lateral sclerosis and two to three confirmed cases of ALS per month documented in Neurology in-patient record & out-patient clinic.

Statistical analysis:

Statistical analysis was done with the SPSS soft ware (version 17, SPSS). Mean and standard deviation of the fractional anisotropy (FA) at different ROIs places were calculated for the patients in the two groups. The DTI indices in patients with Amyotrophic lateral sclerosis (ALS) were compared with the normative data. The Levine's test for equality of variances was applied after which 2-tailed t-test was used for calculation of the p values to see if there were significant differences in the DTI indices within the patient group (ALS) when compared with the normal data. The correlation between the DTI indices and the disability scores in ALS patients was done using Pearson's correlation and scatter plots. Nonparametric tests for independent variable - Kruskal-Wallis test and Mann-Whitney U tests were used in analyzing relation between ALSFRS-R scores and FA values against cognitive variables.

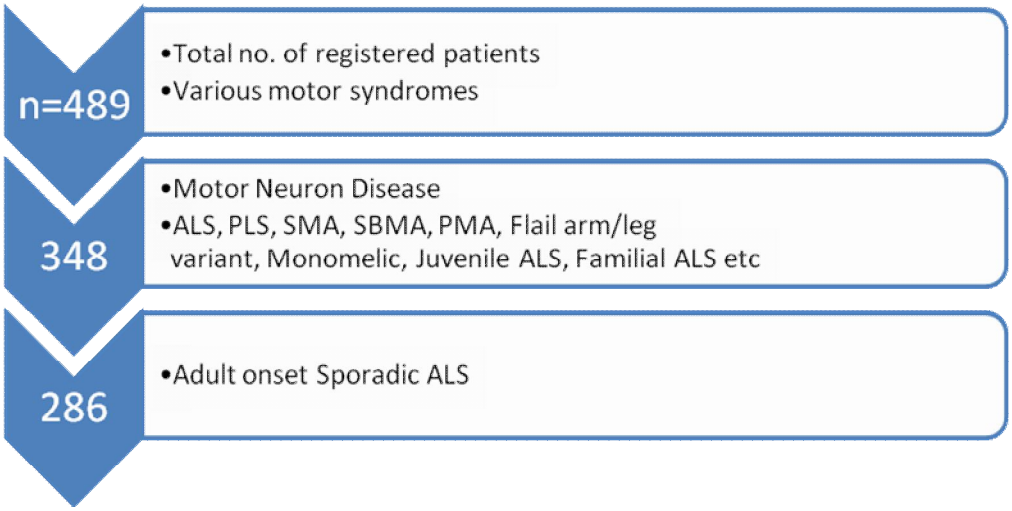
RESULTS

RETROSPECTIVE GROUP:

Baseline Characteristics:

1. In the retrospective analysis, after search through our database of last 10 years, a total of 489 cases were registered (“motor neuron disease”, “pure motor syndrome”, “Amyotrophic lateral sclerosis”, “Motor Axonopathy”, “spastic quadriparesis with UMN and LMN"). Out of these, excluding the ALS mimics, pure LMN variants, Juvenile ALS, Familial ALS and accounting for the insufficient data - 286 Sporadic ALS cases were taken for analysis. (Fig. 5)

FIG 5



2. Approximately 75% of these were males and 25% were females. (Table-2)

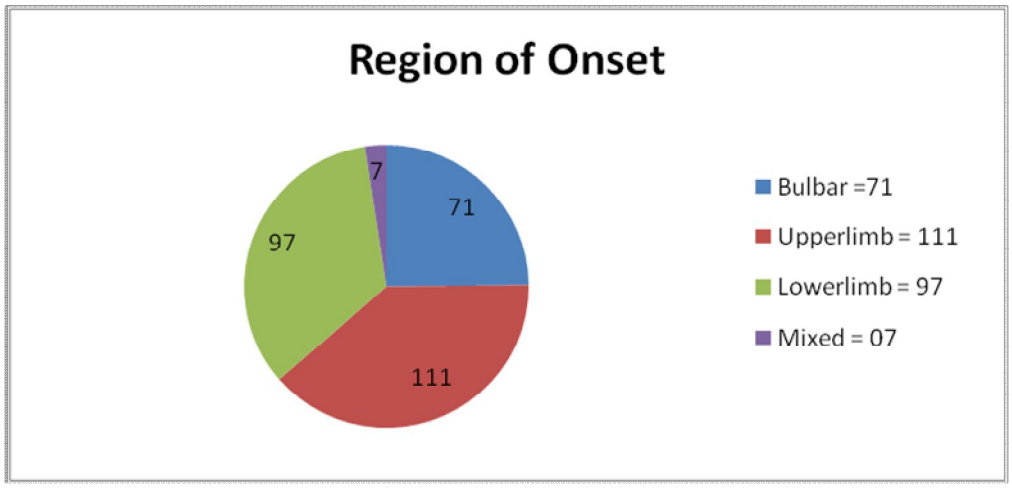
Table -2.

	Frequency	Percent
Males	215	75.2%
Females	71	24.8%
Total	286	100%

3. These 286 cases range from 25yrs to 74yrs, mean of 48.7yrs.

4. The mean duration of illness at presentation was 16 months. (min: 1month, max: 120months)
5. The onset of illness was in Bulbar region in 25% (n =71), Upper limb in 39% (n = 111), Lower limb in 34% and Mixed in 2% cases. (Fig. 6)

Fig 6



6. A significant proportion of patient with bulbar onset had rapid progression as compared to limb onset (p = .03). Mixed onset also had rapid progression. Lower limb onset had slower rate of progression. (Table-3)

Table-3. The Pattern of Onset & Pattern of Progression

		Pattern of Progression			Total
		Rapid - second region within 1 month	intermediate - second region b/w 3-6 months	slow - second region after 6 months	
Pattern of Onset	Bulbar	13	37	21	71
	upper limb	10	81	20	111
	lower limb	6	57	34	97
	mixed	3	3	1	7
Total		32	177	76	286

7. In most of the patient there was contiguous spread of regions for example Upper limb to lower limb and then to bulbar and finally respiration. Similarly, bulbar onset will progress to upper limb and then to lower limb. Few cases progressed by skipping a region also. (Table-5)

Table-5. The pattern of Progression

UL → LL → Bulbar	111 (38.8%)
LL → UL → Bulbar	92 (32.2%)
Bulbar → UL → LL	67 (23.8%)
LL → Bulbar → UL	06 (2.1%)
UL → Bulbar → LL	06 (2.1%)
Bulbar → LL → UL	03 (1%)

8. Approximately, 24% were hypertensive and 11% were known diabetic.

9. Around 27% of patients were smoker and 12% used to consume alcohol.

10. A few of them had exposure to miscellaneous toxins before diagnosis, esp. Heavy metals like lead, cadmium etc (5.2%) and few to chronic organophosphorus compounds (5.6%). Whereas, exposure to native medications (which have a base of heavy metals) after the diagnosis as an alternative therapy, was seen in 28% of cases.

11. A history of weight loss was present in all patients except 2. Around 40% (n=113) had history of mild weight loss (<5kgs), 55% (n=158) had moderate weight loss (5-10kgs) and 5% (n=13) had severe weight loss (>10kg).

12. Higher mental functions and cognitive analysis was limited to bedside tests namely – MMSE (Mini Mental Status Examination) and FAB (Frontal Assessment Battery). The mean MMSE score was 27.9. Around 7% showed abnormalities on FAB.

13. Head drop was seen in 5% of patients. 7% had bladder problems in the form of urgency; hesitancy etc. 5% had extrapyramidal signs on examination.

14. Myokymia was evident in 13%. There was significant correlation with exposure to toxins (native medications, Organophosphates, Miscellaneous toxin exposure) and presence of Myokymia on examination. The duration of exposure to native medication was around 2 – 5 months (mean 3 months).

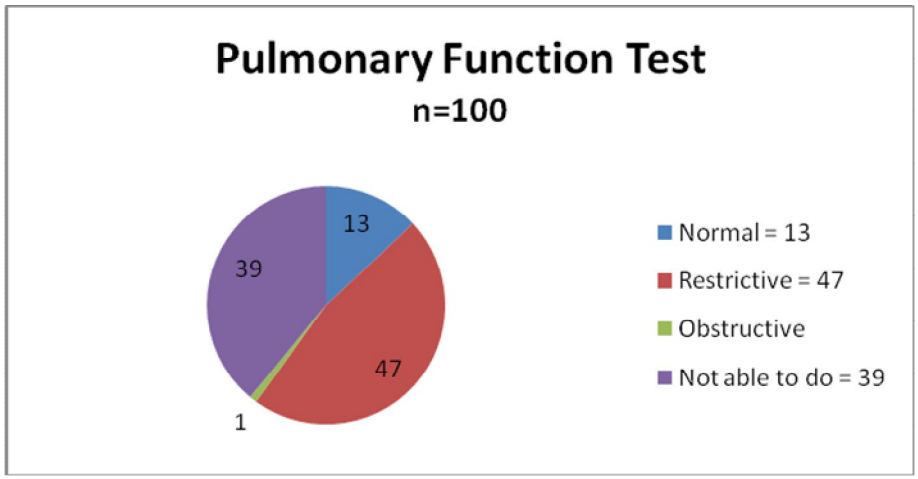
15. Sensory abnormality on examination was seen in less than 5% but abnormal SNAPs were evident in approx. 15% of cases. Out of these patients, 4 underwent Sural nerve biopsy which did not show any significant abnormality.

16. Conduction block (at non-entrapment sites) was seen in 8.3% (n=22) across C8 root. Only 2 of these had response to therapeutic trial with Immunomodulation.

17. Pulmonary Function Tests:

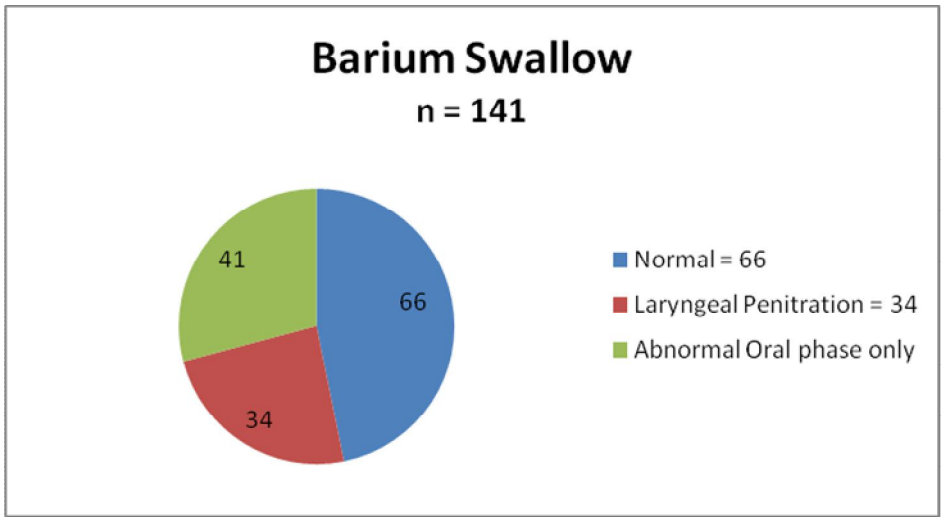
Data was available for 100 patients. Among them 13% had normal results and 47% had restrictive defect. About 39% were unable to perform because of severe bulbar weakness or bed-ridden state. (Fig. 7)

Fig 7



18. Barium Study was performed in 141 patients. Abnormal swallowing with laryngeal penetration was seen in 34 of them, out of which only 5 underwent PEG (Percutaneous Endoscopic Gastrostomy). (Fig. 8)

Fig 8



19. Targeted investigations showed High CSF proteins in 20% of patients. The range of CSF protein was mild to moderate and none had more than 100mg%.

20. Less than 5% had autoimmune markers in their sera like ANA, ANCA, CRP, Complements (C3, C4). The commonest marker present was ANA.

21. CPK was done in 109 patients (38%). There was mild to moderate elevation seen in 30% but none had significant elevation (>10 times the normal).

22. MRI Cervical Spine was done in 259 patients. Only 4 cases (1.4%) had abnormal signals in the cord (**Fig 9)**. MRI Brain was available for 231 patients. It was normal in 38% and showed abnormal signal along the corticospinal tracts (posterior limb of internal capsule, cerebral peduncles) in 12%.

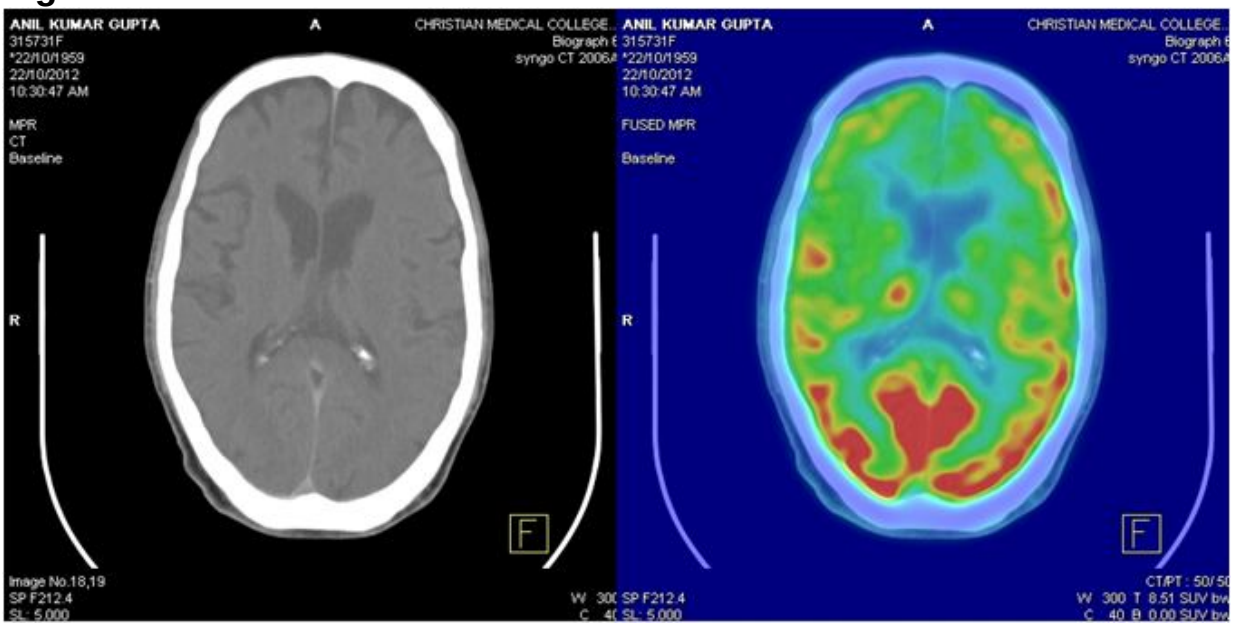
Fig 9.

23. Trial of therapy including pulse Cyclophosphamide was given in 52 patients, out of which 4 had response.

24. PET CT data was available for only 14 patients. Out of these only 2 showed abnormal Brain metabolism – mainly frontal region hypometabolism. (Fig. 10)

PET CT showing hypometabolism in bilateral frontal region

Fig 10



25. The outcome analysis showed that 4 patients had in-hospital mortality.
26. Follow up data at **3 months** was available for 59 patients (21%). Out of this, 10 died, 40 worsened (ALSFRS-R) and 9 had no significant change in ALSFRS-R scores.
27. Follow up data at **6 months** or later was available for 48 cases (16.8%). Out of this, 10 died and 36 worsened.

28. There was no significant correlation between pattern of onset and mortality (follow up at 3 months, p = .418; follow up at 6 months, p = .225). In other terms, 14% of bulbar onset cases either worsened or died at 3 months as compared to 18% of limb onset (UL + LL). This difference is due to difference in rate of progression. Most of the limb onset patients who worsened had involvement of bulbar region within a year of onset. Whereas the around 30% of bulbar onset had slow progression and remained confined to bulbar region even after 1 year of onset (second follow up). From this we also infer that not all bulbar onset cases progress rapidly to respiratory dysfunction, but a significant proportion of them actually remains confined to bulbar symptoms only.

29. The correlation between rate of progression and outcome was significant. 26% of rapid onset cases either worsened or died at 3 months as compared to only 16% of intermediate/slow onset ones. At subsequent follow up (6 months or later), this difference is even more.

    Thus, onset in a region does not necessarily imply worse prognosis but the rate of progression definitely affects outcome. In the table given below, despite onset in bulbar region, 4 patients did not worsen at 3 months but as the duration of the disease increases, the drop in ALS functional scores becomes conspicuous. At second follow up (at 6 months or later), most of the cases show worsening. (Table 6)

Table-6.Summary of ALSFRS-R scores at follow up visits

ALSFRS-R →	Same			Worsened			Deceased			Total
	B	U	L	B	U	L	B	U	L	
At Discharge								2	2	4
F/U at 3m	4	2	2	7	17	15	3	3	3	56
F/U at 6m	1	0	1	6	16	14	2	2	6	48
Total →	10			75			23			

B – Bulbar, U – Upper limb, L – Lower limb

30. Diagnostic Categories: 182 patients were categorized as “Clinically definite ALS” according to Awaji criteria where as 87 of these were clinically definite according to El Escorial criteria. Thus supporting the notion that Awaji criterion increases the sensitivity of diagnosis. The sensitivity of Awaji Criteria was 68.2% and specificity was 86.9% where as sensitivity of El Escorial criteria was 41.6% and specificity 89.6%. Around 30% cases jumped from one category to a higher category on application of Awaji criteria.(Table-7 & 8)

Table-7. Comparison between the two Diagnostic Criteria

Diagnostic Category → / ↓		Awaji Criteria			Total
		Clinically Definite	Clinically Probable	Clinically Possible	
El Escorial Criteria	Clinically Definite	88		0	88
	Clinically Probable	94	67	2	163
	Clinically Probable lab supported	1	16	9	26
	Clinically Possible	0	3	6	9
Total		182	87	17	286

Table-8. Sensitivity & Specificity of the two Diagnostic Criteria

Awaji & El Escorial Criteria Cross tabulation					
			El Escorial Criteria		
			Clinically definite/Clinically probable	Clinically probable-lab supported/Clinically possible	Total
Awaji Criteria	Clinically definite/Clinically probable	Count	249	20	269
		% within elesco	**Sensitivity 68.2%**	57.1%	94.1%
	Clinically possible	Count	2	15	17
		% within elesco	.8%	**Specificity 86.9%**	5.9%
Total		Count	251	35	286

PROSPECTIVE GROUP:

1. A total of 34 patients fulfilled the inclusion criteria. They were recruited and compared with normative group.
2. 56% (n=19) were male and 44% (n=15) were females.
3. The mean age was 49.7yrs (min: 35, max: 67)
4. The mean duration of the disease at presentation was 22 months. (min: 4m, max: 84m). As the duration of the disease increases, there is worsening of ALSFRS-R scores. (Pearson correlation = -.373, p = 0.030)
5. 20% were hypertensive and 6% were diabetic. The other baseline characteristics are given in the following Bar diagram (Appendix - 8)
6. The region of onset was Upper limb in 15 (44%), Lower limb in 11 (32%) and bulbar in 8 (24%). This was similar to the distribution seen in retrospective group.
7. There was mild to moderate CSF protein elevation in 6 out of 34 patients (17%) (Range 17 u/l to 84 u/l) and positive autoimmune markers (ANA, C3, C4) in 2.

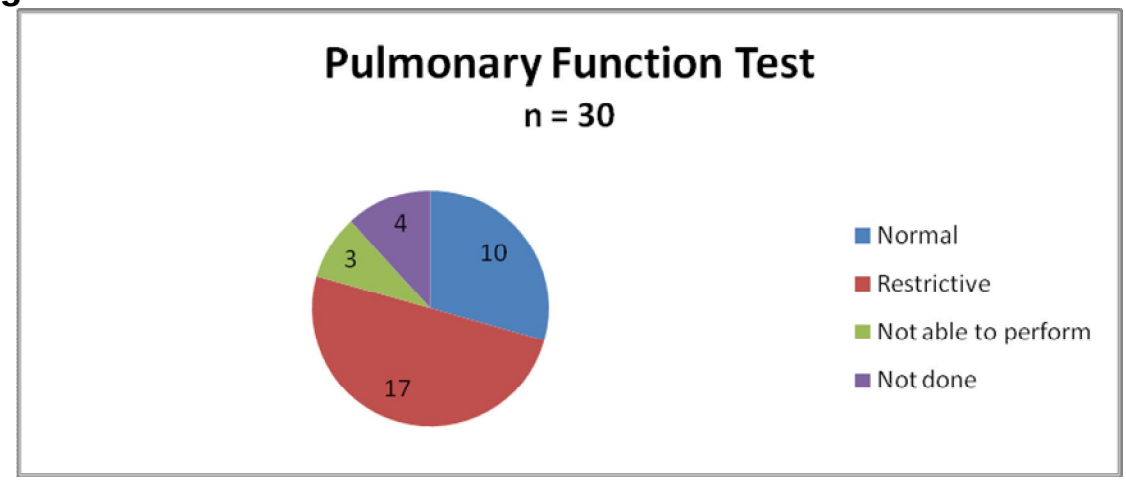
8. Considering the pattern of onset and presentation in relation to history of high physical activity, we found that in all the 9 patients with history of high physical activity (occupation related or contact sports), the onset of the disease was in limbs (5 in upper limb and 4 in lower limb).
9. Neuroimaging: MRI Brain and Spine were done in all 34 patients. None had any abnormality in cervical spinal cord other than age related spondylotic changes without evidence of significant root compression. 6 had abnormal MRI Brain in the form of non-significant scattered white matter changes or old lacunar infarcts. 8 had symmetrical hyperintensities in corticospinal tracts.
10. The pattern of onset and progression is as shown in table given below. 44% (n=15) were upper limb onset, 32% (n=11) were lower limb onset and 24% (n=8) were bulbar onset.
    a. Rapid rate of progression was observed in 2 patients – both of which were lower limb onset.
    b. Slow progression was seen in 2 of the bulbar onset cases – both of these were females and the clinical findings remained localized to bulbar region even on follow-up. (Table-9)

Table-9. Region of onset & Pattern of Progression Cross tabulation

Pattern of progression ➡		Rapid - second region within 1 month	Intermediate - second region b/w 3-6 months	Slow - second region after 6 months	
Region of onset	Bulbar	0	6	2	8
	Upper limb	0	9	6	15
	lower limb	2	9	0	11
Total		2	24	8	34

11. Root stimulation across C8 root was done in 24 of the patients, out of which 5 had evidence of conduction block ranging from 25% to 45%.
12. The diagnostic criteria: Both Revised El Escorial and Awaji criteria were used. Awaji Criteria increased the yield of diagnosis. (91% were clinically definite ALS as compared to 82% with El Escorial criteria)
13. Barium Study was done in 21 patients. 4 of these showed evidence of laryngeal penetration and 2 out of these underwent PEG implantation.
14. PFT was done in 30 of 34 patients. 17 of these showed evidence of restrictive defect with low Forced Vital Capacities.(Fig 11)

Fig 11



15. Phrenic nerve conduction was done in 27 of 34 patients. The latency and amplitude of phrenic nerve conductions were tested against PFT by Kruskal-Wallis test (Nonparametric test for independent variables)

    It showed significant correlation between abnormal PFT and prolonged phrenic latencies ($p = .041$) as well as lower phrenic amplitudes ($p = .044$).

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Phrenic nerve conduction Latency is the same across categories of Pulmonary Function test.	Independent-Samples Kruskal-Wallis Test	.041	Reject the null hypothesis.
2	The distribution of Phrenic Amplitude is the same across categories of Pulmonary Function test.	Independent-Samples Kruskal-Wallis Test	.044	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

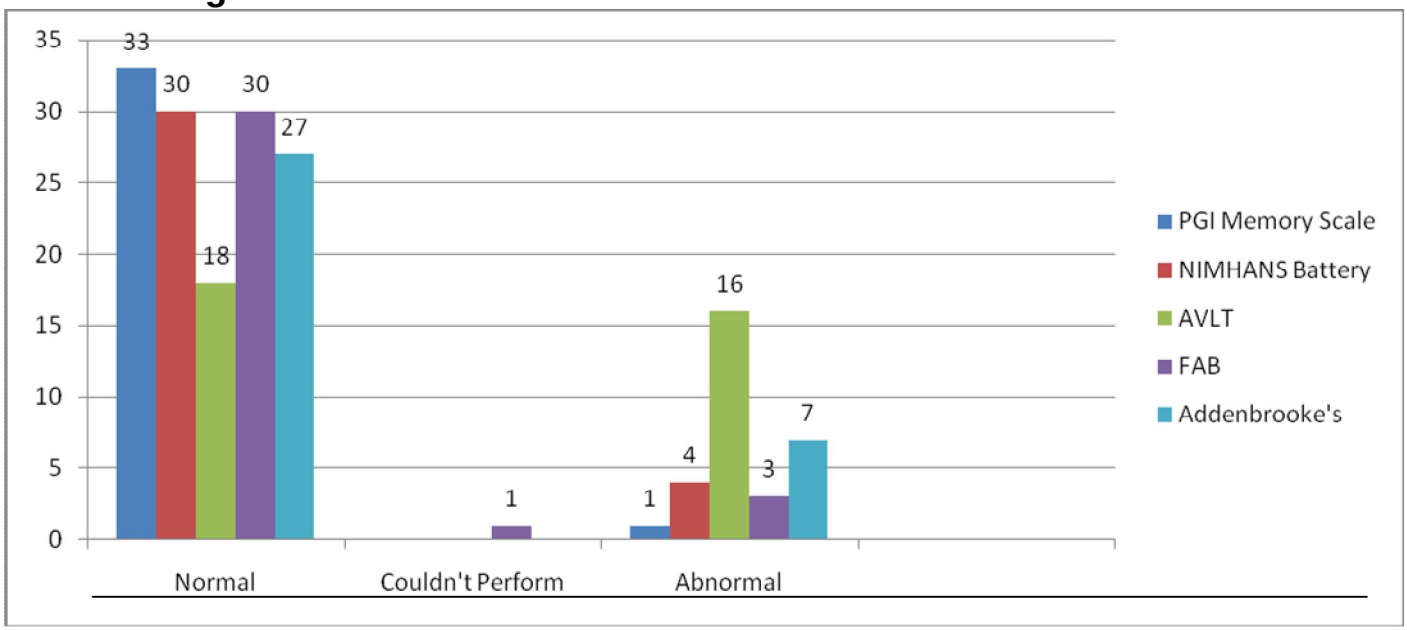
But when PFT was compared with bedside examination of palatal excursion and Gag reflex – there was no significant correlation between the two.

16. Cognitive battery was attempted in all patients. The motor disability and spastic dysarthria was kept in mind while applying and interpreting the tests. Only the batteries which have established age and education based norms were used, namely PGI Memory scale, Addenbrooke's Cognitive Examination- Revised (ACE-R), Frontal Assessment Battery (FAB), and NIMHANS Battery.

    A significant number of patients (47%) showed abnormality in Auditory Verbal Learning Test (AVLT) and few showed evidence of Executive dysfunction (motor and language), and Planning and Judgment – on ACE-R (21%) and FAB (11%) (Fig.12)

Cognitive Assessment

Fig12



AVLT – Auditory Verbal Learning Test, FAB – Frontal Assessment Battery

17. Follow up data was available for 50% of cases. At first follow up (3 months), 5 out of 17 patients showed no or minimal change in their functional status (ALSFRS-R). At subsequent visits, all patients showed worsening except one. (Table-11)

Table-11.Comparison of ALSFRS-R Scores at first & second follow up

	F/U at 3 months	F/U at 6 months
No follow up	17	21
ALSFRS-R Same	5	01
ALSFRS-R worsening	12	12

18. Therapeutic trial with Immunomodulation was given in 20 of the patients, out of which 1 showed response.

19. DTI indices for normative group given in *Appendix 10*.

Table-12. DTI indices in Amyotrophic lateral sclerosis:

DTI indices in ALS patients and their correlation with normal data:

ROI	FA – Normative Group	FA – ALS patients	**p value**
Right PLIC *	0.67 ± 0.05	0.64 ± 0.05	**0.010**
Left PLIC *	0.69 ± 0.05	0.64 ± 0.03	**0.000**
Right Cerebral peduncle	0.71 ± 0.07	0.66 ± 0.05	**0.000**
Left Cerebral peduncle	0.74 ± 0.05	0.70 ± 0.05	**0.010**
Right pyramid	0.58 ± 0.06	0.50 ± 0.05	**0.000**
Left pyramid	0.58 ± 0.06	0.50 ± 0.05	**0.000**
Right subcortex	0.58 ± 0.06	0.50 ± 0.05	**0.000**
Left subcortex	0.58 ± 0.05	0.50 ± 0.07	**0.000**

Table-13. Correlation of disease severity (ALSFRS-R) and DTI indices: Pearson correlation of the ALSFRS-R scores with FA:

ROI	**Fractional Anisotropy**	
	Pearson Correlation	**p value***
Right PLIC	-0.099	.577
Left PLIC	-0.011	.951
Right Cerebral Peduncle	-0.087	.625
Left Cerebral Peduncle	-0.171	.332
Right Pyramid	0.071	.690
Left Pyramid	-0.121	.495
Right Subcortex (at the region of the CST *)	0.038	.830
Left Subcortex (at the region of the CST *)	-0.165	.230

* p value: significance was calculated using the 2 –tailed t tests
* CST- corticospinal tract, subcortical white matter just below the motor cortex
A Pearson correlation was computed to assess the correlation between the DTI indices and ALSFRS – R which showed that there was no statistically significant correlation. (p value > 0.05).

20. The DTI indices were compared against the cognitive scores. Significant correlation between low FA values and abnormal cognitive scores were seen at two ROI – Left Cerebral Peduncle (p = .021) and at Right Pyramid (p = .006) (Table-14)

Table 14 Correlation between DTI Indices and Cognition

DTI Indices (FA)	Chi Square	p value
Right Subcortex	0.005	0.946
Left Subcortex	2.016	0.156
Right PLIC*	0.370	0.543
Left PLIC*	1.553	0.213
Right Cerebral Peduncle	1.484	0.223
Left Cerebral Peduncle	5.039	**0.021**
Right Pyramid	8.497	**0.006**
Left Pyramid	0.658	0.417

PLIC – Posterior limb of internal Capsule

20. ALSFRS-R scores were also compared with cognitive scores. There was no significant correlation between the two. (Table-15)

Table 15 Correlation between ALSFRS-R scores and Cognitive Scores

Cognitive Battery	Chi Square	p value
P.G.I. Memory Scale	10.333	0.666
Frontal Assessment Battery (FAB)	18.167	0.151
Addenbrooke's Cognitive Examination - Revised (ACE-R)	12.056	0.523
NIMHANS Cognitive Battery	14.612	0.371
Auditory Verbal Learning Test (AVLT)	14.040	0.332

DISCUSSION

Retrospective Group:

The natural history of ALS has been studied in various parts of the world. In our study, the retrospective cohort comprised 489 consecutive patients with motor predominant neurological disorder. Out of these 286 cases of sporadic ALS from 2002 to 2012 were included in analysis. This was a very heterogeneous group.

The gender distribution in this cohort was male predominant. Approximately 75% were male. This is similar to findings in other epidemiological studies (1). The mean age at presentation was 48 years which is almost a decade younger as compared to western data (10, 55).

This fact can be attributed not only to genetic factors specific to our geography but also to environmental and host of other factors like exposure to toxins, heavy metals, native medication, fertilizers and insecticides. In this study about 5% patient had exposure to heavy metal toxins and 5% to chronic organophosphorus compounds. 28% of cases in retrospective study and 50% in prospective group were exposed to native medication as a means of alternative therapy for a minimum period of 3-6 months, at some point of time after diagnosis. Presence of myokymia on examination provokes us to elicit history of such exposures which serve as a “second hit” and may be causative in rapid rate of progression. There is no direct etiological correlation that has been proven but few studies from India describe similar exposure history in young patients with ALS (9), 91). The exposure to toxic substances and organophosphorus compounds is usually occupation related. The population affected by this is mostly rural, low education status

and very few use protective gear/clothing at their work places. Lack of personal awareness combined with lack of social and industrial initiative (for eg. Waste management) is a possible etiological factor and thus, a potential area which need urgent attention.

This study found a trend towards younger age at onset and faster progression was seen among these cases that have been exposed to environmental toxins. There was a significant correlation ($p<.05$) between examination finding of Myokymia and history of exposure to these toxins. There is a significant correlation between exposure history, presence of myokymia and rapid rate of progression ($p = .024$). This fact has not been well documented previously in literature (21).

Around 39% cases had onset in upper limb, 34% in lower limb and 25% in bulbar region and less than 2% had mixed onset disease. The less percentage of mixed onset cases may be attributed to the purely retrospective nature of the study. Otherwise, the distribution of patients is similar to findings in previous study (11)). In most of the patient there was contiguous spread of regions for example Upper limb to lower limb and then to bulbar and finally respiration. Similarly, bulbar onset progressed to upper limb and then to lower limb. This is similar to earlier documented pattern in literature (55). Few cases of spread by skipping of region were also seen, esp. lower limb to bulbar region. No major difference in rate of progression of disease was observed in this category. Fujimura et al (55) found 15% of cases of lower limb onset ALS spreading from lower limbs to bulbar skipping upper limbs. They also documented 37.5% of bulbar cases skipping to lower limbs. Similar to our study, they also didn’t find any significant difference in functional

scores or prognosis in these patients unless bulbar region is involved within 12 months of onset.

It was possible to know the subsequent site of involvement with certainty in 73% of cases (*n* = 209). In approx. 72% cases, it was the contralateral limb that got involved next, whether the onset was in upper limb or in lower limb. That means spread was from one lower limb to next or from one upper limb to contralateral upper limb in 72% of cases. Turner M. R. et al found similar findings in their study on lower limb onset ALS where they documented initial progression either to the contralateral leg (76%) or ipsilateral arm (24%) (95). But this was not the case in study by Fujimura et al (55) in which they found 65% patients progressing from upper limb to lower limb or from lower limb to upper limb rather than contralaterally.

In 15%, the ipsilateral arm or leg got involved depending on the region of onset – leg or arm, respectively. In rest of the 15%, the symptoms became more or less generalized after onset in a limb. This is different from what is documented in literature (95). Longitudinal studies of ALS have shown that the region of onset is the most severely affected, with spread towards the contiguous body regions, and that LMN and UMN loss occur independently of each other (96, 97). We, like others, observed in this study that sequential spread supports the concept of focal onset and radiating involvement of LMNs.

The time taken from onset of first symptom to reach second symptom (O-SS) was variable (ranged from 1 month to 16 months). The median time was 6 months. The mean ALSFRS-R scores of cases with O-SS < 6 months was higher than in those with O-SS > 6 months (38.34 & 31.57 respectively). Although p value was > 0.05, this showed a clear

trend that time taken to acquire second symptom / region is an indicator of poor prognosis. Similar conclusions were drawn by Turner et al and Fujimura et al also (55, 95).

A statistically significant number of cases with bulbar onset had rapid progression as compared to limb onset ($p < .05$). This is in concordance to evidence in literature (55). Unfortunately, due to retrospective nature of the data, time to onset of respiratory dysfunction and cause of demise in most of the cases was not known. Also a higher number of females had bulbar onset as compared to males (31% & 22%, respectively). Studies also mention higher percentage of females as compared to males with bulbar onset ALS (10).

The neurological examination at presentation was obviously a mixture of UMN and LMN findings. The pattern of weakness was distal to proximal in 94% of cases. Around 60% of patients at presentation had distal wasting in both upper and lower limbs. These were mainly of limb onset cases that were at least 4 months into the illness. As compared to these, the phenotype in bulbar variants was that of mild distal upper limb wasting with tongue atrophy and lower limb spasticity. No gender and age predominance was seen in this group although the progression was found to be slower. Reviewing literature, in the pure bulbar palsy phenotype typically affects women older than 65 years of age, the disease remains localized to oropharyngeal musculature and UMN features predominate (13).

UMN predominant presentation i.e. “spastic quadriparesis” or “spastic syndrome” was seen in approximately 32% cases (n = 91). Their age distribution is as follows:-

Table 16 Comparison of early and late onset UMN Predominant ALS

Age in years	Total no. of cases	Cases with predominant spasticity	Mean ALSFRS-R scores
25 – 40	77	19 (25%)-17 males, 2 females	38.564
> 40	209	72 (35%)-48 males, 24 females	31.675

Predominant spastic presentation was seen in all age groups. But gender distribution was suggestive of male predominance in age between 25 – 40 years. The mean ALSFRS-R scores were higher in younger age group. Studies have shown that young ALS presents with predominant UMN features and the rate of progression is slower in this group with higher mean ALSFRS scores, that is consistent with our findings also (98).

Weight loss was observed in almost all cases. The correlation between severity of weight loss and rate of progression or the site of onset was not significant. Although, a very few of our patients were obese (3%), 8 out of 9 of them had slow progression. This finding is similar to earlier findings which lead to notion that over-weight and obesity can be protective of rapid progression of illness (92, 95).

The various extra-motor features observed were bladder involvement in 7% and extrapyramidal signs in 5%. These were in concordance with known prevalence of non-motor or extra-motor features in ALS (40, 100).

Severe neck muscle weakness was present in around 17% of cases and 5% had historically and clinically “dropped-head-syndrome”. This percentage is higher as compared to earlier studies (101) that have reported a prevalence of 1.3%. The age was

evenly distributed throughout the sample. This is also similar to the findings in literature (97). In most of these cases, there was of proximo-intermediate weakness and wasting of upper limbs. The tone was reduced in upper limbs but increased in lower limbs; a pattern that has been named as “Man in Barrel” appearance. Around 43% (n = 6) cases of these “dropped-head syndrome” had this phenotype.

The revised El Escorial (World Federation of Neurology) criteria for the diagnosis of ALS do not allow abnormal sensory nerve conductions except in the presence of entrapment syndrome or coexisting peripheral nerve disease (87). Other studies have reported abnormal findings of the peripheral nervous system in ALS ranging between 13% and 22% (102, 103, 104, 105). It has been well proven that ALS is not a pure motor syndrome but a heterogeneous multisystem disease with a significant sensory involvement. Thus we analyzed sensory system both clinically and electrophysiologically. Our study suggested that less than 5% patients report sensory complaints but abnormal SNAP (sensory nerve action potential) were seen in as many as 15%. In all the cases minimum four pair nerves were analyses (2 pair in upper limbs – median & ulnar; and 2 pairs in lower limbs - superficial peroneal & sural). Sometimes radial nerve conduction in upper limbs was also done depending on the pattern of weakness and to differentiate from Brachial plexitis. Most of the patients with sensory complaints had normal sensory conductions whereas most of the patients with abnormal sensory conductions had no sensory complaints. 26% of them had diabetes and 26% consumed alcohol – both are potential confounding factors. But in none of the cases the pattern of involvement was in keeping with distal symmetric polyneuropathy (DSP) which is usually seen in Metabolic (like diabetes) or toxic neuropathy.

Four cases also underwent nerve biopsy – 3 out of which were reported normal (sural nerve). Vasculitic like changes on histopathology of nerve biopsy have been documented in ALS (20, 106) which was not present in our case.

The pathogenesis has been subjected to wide variety of speculations. Heads et al suggested that the primary pathology in the sensory peripheral nerve in ALS is dorsal root ganglion neuronopathy, resulting initially in progressive axonal atrophy followed by secondary demyelination and ultimately by axonal loss (107).

Conduction block is an exception to the electrophysiological diagnosis of ALS. In our study, 8.3% cases had evidence of conduction block apart from entrapment sites. Mainly these were present on cervical root stimulation. Other co-morbidities like diabetes and paraproteinemia were absent. Serological evidence of Anti Ganglioside antibodies was absent (tested in 3% of cases). The clinical phenotype of these cases didn't differ from classic ALS except for 2 patients who responded to trial of immunosuppressive therapy. This is in contrast to earlier defined phenotypes of these patients – of being more LMN predominant, slower progression and longer survival (61). Thus, many a times we find mixed cases in which inflammatory/autoimmune causes co-exist along with primary neurodegenerative pathology. These cases warrant immunotherapy and if given adequate trial, will respond to treatment.

Autoimmune panel and markers of Vasculitis were available in 78% but positive only in 2% (ANA, ANCA, Complements C3, and C4). Most of the studies of ALS provide some evidence of autoimmune mechanisms associated with the disease but it is not clear whether these alterations are pathogenic or a nonpathogenic epiphenomenon (108).

Most of the trials of immunosuppressive therapy in ALS have failed to show any significant response (109). Our study corroborates this fact further. 52 patients were given adequate trial with pulse Cyclophosphamide therapy but only 4 responded to it. The responses were more subjective than objective and can hardly be documented in terms of functional scale. No difference in survival outcomes were seen in those who responded to those who didn't.

It has been well established that cognitive dysfunction is a part of spectrum in ALS. But it is not that all patients will show cognitive abnormality. In most of them, even if we find any abnormality, it will be subtle. These evidences come after applying elaborate neuropsychiatric and cognitive scales. Approximately 30 - 50% of cases will have some cognitive dysfunction (50) even though they don't fulfill the criteria for dementia. Up to 15% of cases can be diagnosed as dementia (52, 110). The most common cognitive dysfunction is predominantly of dysexecutive in nature. The most common type of dementia known among ALS patients is behavior variant Frontal Temporal Dementia (bvFTD) (16). In the retrospective analysis, we found around 28% of cases showing abnormality on bed-side preliminary cognitive batteries like MMSE and frontal assessment battery (FAB). Out of these approximately 7% showed abnormal scores in most of the categories of the tests, and had unequivocal evidence of cognitive involvement. Most commonly, lexical fluency followed by conflicting instructions and go-no-go task were affected. This shows that frontal executive, set-shifting and motor-planning are affected and can be found even by means as simple as bed-side FAB, without need of elaborate scales, psychologists, psychiatrists etc. This has bearing not only on documentation and enrichment of epidemiological records but a direct effect on

management of an individual. Obviously, to label someone has having dementia, one needs fulfillment of complete criteria. These have been looked into in a small set of people (n = 34) in prospective analysis. There was no correlation between MMSE scores and abnormality on FAB and mean MMSE was 27. The group was heterogeneous in respect to the education status. Education is the most dominating confounding factor. 58% of cases with poor education status (primary school and below), showed abnormality in FAB scores where as 84% of those who went to college or attained higher education scored normal on FAB. Although, statistically insignificant, there was a trend towards worse FAB scores as the duration of the disease increases. Despite insufficient data, one can derive a strong relation between abnormal frontal executive tests and advance ALS, keeping in mind one's education status and duration of disease. The other potential confounding variables are spastic dysarthria in cases of abnormal lexical fluency.

In this study, we had data on Barium study for 49% of cases (n = 141). Out of these, abnormal study was reported in a total of 53% and laryngeal penetration and high tendency to aspirate was seen in 24% of cases who underwent the study. 77% of bulbar onset cases of who underwent barium study showed abnormality as compared to 38% of limb onset cases. This was statistically significant (p = .05). There was a statistically significant correlation between worse ALSFRS-R scores and abnormal barium study (p = .007). This has been proven in earlier studies too (7, 57) that one of the main prognostic factors in any given setting is bulbar dysfunction. This also has direct bearing on quality of life, social health and depression (111). Pseudobulbar sign (exaggerated gag reflex) was seen in 45.5% of cases. 50% of these were emotionally labile.

Only 5 patients underwent Percutaneous Endoscopic Gastrostomy (PEG). Gastrostomy is one of the only management options that makes a significant difference in outcome and survival (46). It is safe and effective measure to prevent malnourishment, weight loss and aspiration. It can be done by interventional radiologists as well as by gastroenterologists (112). Management options in any bulbar ALS includes altering the texture of diet for bolus control purposes, compensatory swallowing strategies, changing eating habits (e.g., smaller portions, increased mastication time), and consideration for early PEG implantation (113).

The data for pulmonary function test (PFT) was available for 100 patients (35%). Among them 86% had abnormal results (39 were not able to perform and 47 had restrictive pattern). Most of these were bulbar ALS cases (31%). The mean ALSFRS-R score in patients “unable to perform” PFT was 25, in patients with “restrictive defect” was 31 and in patient with “normal PFT” was 38. All the patients who died before discharge from the hospital had severe respiratory dysfunction (57, 114). Thus PFT is a cheap and good tool to prognosticate any patient with ALS. It can also be a effective monitoring tool as it’s a direct measure of one’s functional state, quality of life and thus, can significantly affect management options (115). But it is hard to interpret PFT in patients with severe bulbar weakness without limb involvement or in patients who are bed ridden without respiratory involvement. Most of these cases are not able to complete the test and PFT is not a good tool in these set of patients. Investigations and management have to be individualized. PFT can be correlated with phrenic nerve conduction parameters for early prediction of patient likely to end up in respiratory embarrassment (116). Unfortunately,

phrenic nerve conduction parameters were available only for 13 patients in retrospective group.

CPK (Creatine phosphokinase) is raised in around 40% of cases of sporadic ALS (112). In our study, CPK values were known for 109 patients with a mean of 103 U/L. There was no significant correlation between CPK values and ALSFRS-R scores ($p = .687$). Earlier studies also have shown the similar results (117, 118).

MRI of cervical spine and brain are done to rule out close mimics like cranio-vertebral junctional abnormalities, high cervical cord demyelination, parasagital lesions, adrenoleukodystrophy. Except for 1.4% of cases, the rest showed normal cervical spine or insignificant cervical spondylotic/degenerative changes. In 12% of cases abnormal signals along corticospinal tracts (CST) was noted – posterior limb of internal capsule and cerebral penduncles. These abnormalities are observed frequently in normal patients and thus considered unreliable and inconsistent, and they do not correlate with clinical scores. T2-hyperintensity of the CST has low sensitivity (approximately ≤40%) and low specificity (approximately ≤70%) (20). FLAIR images increases the sensitivity on the cost of reduced specificity. Proton density images are not routinely used but said to have a better sensitivity as well as specificity in detecting abnormality in CST in ALS patients, esp. early into the disease. Newer techniques like Voxel based morphometry (VBM) and T1-weighted spin-echo magnetization transfer contrast (T1 SE MTC) have even higher sensitivity (80%) and specificity (100%) (119)

The follow up data was available for 21% (n = 59) at 3 months and for 16.8% (n = 48) at 6 months or later. ALSFRS-R scores showed worsening at 3 months and later. Those

with bulbar onset and advance age at onset had faster progression and lower ALSFRS-R scores at follow up. The mean ALSFRS-R scores for patients above 60 years of age at first follow up was 27.93 and second follow up was 21.34. There was a significant difference in the ALSFRS-R scores at both the follow-ups between bulbar onset and limb (both upper and lower limb) onset cases (p = .032). Mortality ratio at second follow up was higher than first follow up but due to small number, it was not statistically significant. These findings are in concordance with other natural history studies (55, (120). Due to smaller number of cases above 60 years, the difference between ALSFRS-R scores at presentation between relatively young onset and late onset was not statistically significant. Although mortality was higher in group aged > 60 years, multiple systemic factors & co-morbidities were present that could confound this result.

The two diagnostic algorithms were compared, namely Revised El Escorial criteria and Awaji-shima criteria. Both clinical and electrophysiological data were looked at. According to Awaji criteria, 64% patient fell into “clinically definite ALS” as compared to 31% when El Escorial criteria were used. Thus sensitivity of the diagnostic algorithm was increased as was shown earlier (88), (89). The sensitivity of Awaji Criteria is 68.2% and specificity is 86.9% where as sensitivity of El Escorial criteria is 41.6% and specificity of 89.6%. Applying the Mcnemar test (p = .001), about 30% of individuals shifted one category up the diagnosis ladder from El Escorial diagnostic categories. The measure of agreement kappa = .540.

PROPECTIVE STUDY

In the prospective group, there were 34 patients. Their demography of the group and that of normative group was comparable without confounding or selection bias (*Appendix-8*). The distribution of males and females were almost equal (55% & 45%). The mean age was 49 years similar to retrospective group.

The site of onset was upper limb in 43%, lower limb in 34%, and bulbar in 23%. This is similar to the pattern observed in retrospective group and other studies. The ALSFRS-R scores at presentation did not differ with region of onset. Contrary to what is known, at first follow-up, the scores were worse in upper limb onset cases as compared to bulbar onset ones. Studies done in west have shown worse scores with bulbar onset as compared to limb onset ALS (25), 42). Lower limb onset cases had higher ALSFRS-R scores and the progression was also slower (statistically significant difference between scores at 1st follow up).

Table 17 **ALS variants and comparison of serial functional scores**

Phenotype ↓	**Number of patients n = 34**	**ALSFRS-R at presentation (mean)**	**First Follow up**	**Second Follow up**
Classical ALS	17	34.65	29.23	19.34
Pseudopolyneuritic	3	35.26	34.22	30.39
Man-in-barrel	2	30.47	29.87	28.98
Predominant UMN	6	36.58	33.27	30.76
Predominant Bulbar	4	38.69	37.19	33.78
Hemiplegic Variant	2	29.87	26.65	23.71

The pattern of spread found in prospective group was different from observations in retrospective group. Excluding the 8 cases of bulbar onset and 3 cases in which data was insufficient – the rest of the 23 cases were analyzed. 15 cases had spread to ipsilateral side and 8 cases to contralateral side (accounting for both upper limb onset and lower limb onset cases). In retrospective group, the most common pattern of spread found was contralateral i.e., one upper limb to contralateral upper limb followed by lower limbs. But in prospective group, 45% cases first spread to ipsilateral limb (right upper limb to right lower limb) and only then went to contralateral side. Similar pattern has been documented by Fujimura et al where most of their cases spread from upper limb to lower limbs (55).

Few cases with “skip-pattern” of progression were also present. It was interesting to observe that those who jumped from bulbar to lower limb had slower rate of progression (spread to subsequent site after 12 months) whereas those who jumped from lower limb to bulbar within 1 year had rapid rate of progression (spread to subsequent site within 1-3 months or involvement of respiration). These few cases can give us insight into the pathogenesis of neuronal death – whether it occurs simultaneously in all regions or spreads contiguously from one region to other; whether the spread is centrifugal or goes outwards, like many earlier studies have postulated. This also shows that clinical presentation of an individual with ALS is not a direct representation of pathology at molecular level. Environmental and genetic factors also play a vital part in deciding the rate of progression, the spread and clinical phenotype. Obviously, when we see a patient in clinic, he is outcome of all the demographic, environmental and genetic factors. When we see a patient with ALS in later stages, the pathological state has already become

confluent. It is relatively easy to speculate retrospectively the nature of the disease but when a patient comes early into the illness, except for few known poor prognostic markers, it is very difficult to predict at what rate he will progress and what will be the next symptom. Only time can prove or contradict our predictions deriving a strong case for stringent and regular follow up.

Amount of physical activity in premorbid life has been postulated to be a risk factor for developing ALS. The origin of this idea came from studying batting averages of Lou Gehrig just before he was diagnosed as ALS (121). 9 cases in this study had history of heavy physical activity (6 cases were occupation related and 3 had history of contact sports). The rate of progression or ALSFRS-R scores was did not correlate with history of heavy physical activity ($p = .956$). This is similar to findings in literature (121). Veldink et al (122) showed that amount of physical activity is not related to rate of progression and neither to functional scores.

Turner et al (123) hypothesized that in most of the upper limb onset cases, the limb of onset was dominant one. But in lower limb onset cases, no such relation could be seen. Since routine physical demands on the upper limb are heavily influenced by limb dominance, whereas in the lower limbs the commonest function is standing or locomotion, which uses both legs equally. However, there may also be an inherent cortical vulnerability underlying upper limb-onset laterality, possibly influenced by changes in neuronal connectivity and cortical excitability in relation to handedness and reflected by the "split hand" phenomenon consistently observed in ALS.

The cognitive analysis comprised of 2 qualitative tests (FAB and ACE-R) and 2 quantitative tests (PGIMS and NIMHANS Battery). The scores were compared with normative data (*Appendix-7*). The motor disability and spastic dysarthria was kept in mind while applying and interpreting the tests. Around 47% showed abnormality in at least one qualitative and one quantitative battery. But due to small sample size, the scores were heterogeneous and no one particular test came up as representation of cognitive abnormality in ALS. A rough generalization, though, could be made. Most of the patients showed abnormality in three spheres – Language (lexical fluency) seen in 35% of cases, execution, set shifting and planning (motor programming) in 25% of cases, and immediate recall & working memory in 40% of them.

On the other hand, except for 3 patients none showed abnormality in visual memory & recall, visual recognition, long term percent retention (LTPR), construction ability, orientation, and visuo-spatial tests. Only one patient showed behavioral abnormalities and fulfilled Neary criteria for bvFTD (Behavior variant of Fronto-temporal dementia). This is similar to the findings suggested by Phukan et al (110) except that they found significant percent of cases having visuo-spatial abilities also. They studied a much larger group and their demography including age and duration of illness was very different from this group. Murphy et al divided ALS into ALS with cognitive deficits and ALS with behavioral deficits. They found different set of tests which were sensitive and specific for them. They also studied volumetric analysis of whole brain and found right hemisphere atrophy in most of these patients (124).

The focus of most physicians and care-givers is on motor deficits and an emphasis is not made on the behavior and cognitive deficits. But studies have shown (52) that cognitive

profile of any ALS patient affects his management options, the compliance & response to treatment, and quality of life. Thus, demonstrating these extra-motor abnormalities is very essential.

Pulmonary Function Test (PFT) was done in 30 patients. 17 of these showed evidence of restrictive defect with low Forced Vital Capacities. Phrenic nerve conduction was done in 27 of 34 patients. The latency and amplitude of phrenic nerve conductions were tested against PFT by Kruskal- Wallis test individually. It showed significant correlation between abnormal PFT and prolonged phrenic latencies (p = .041) as well as lower phrenic amplitudes (p = .044). But when PFT was compared with bedside examination of palatal excursion and Gag reflex – there was no significant correlation between the two.

When the DTI indices of patients with ALS were compared with the normative data there were lower FA values in all the regions of interest that were evaluated along the corticospinal tract. There was statistically significant correlation using *t test* in the subcortical white matter underlying the motor cortex in the region of the corticospinal tract (p value < 0.001), posterior limb of internal capsule (p value 0.009 and < 0.001), cerebral peduncle (p value <0.001 and 0.01) and the pyramids (p value < 0.001). A Pearson correlation was computed to assess the correlation between the DTI indices and ALSFRS – R which showed that there was no statistically significant correlation (p value > 0.05). The similar correlation was found in other studies too (72, (125). Thus, decreasing FA values along the corticospinal tracts is an objective estimation of UMN dysfunction in ALS. DTI plays a key role in evaluation of UMN involvement in ALS; it can be correlated with UMN scores (124) as well as with central motor conduction time.

The correlation between FA values and cognitive scores were tested with nonparametric test for independent variables (Kruskal-Wallis and Mann-Whitney U test). The result was statistically significant for FA value at right pyramid and left cerebral peduncle against categories of Cognitive scores (p = .006 & p = .021, respectively). The rest of the analysis didn't draw statistically significant result. The reason for this may be several. Firstly, in our study DTI was done mainly to look for abnormalities in corticospinal tracts. The study was not designed to look for DTI indices and their correlation with cognition. For appropriate functional analysis of cognition and behavior, the ROI placement is quite different (extra-motor regions including association and limbic fiber tracts). Secondly, volumetric changes have been documented to have correlation between cognitive dysfunction and DTI changes rather than FA (126).

The follow up data for prospective group was available for 50% of patients at 3 months and for 38% at 6 months. Except for 1 patient, all patients showed worsening on follow up (lower ALSFRS-R scores). The difference between scores at presentation as compared to scores at second follow up was statistically significant (p = .044). The difference between scores at first and second follow up were also significant (p = .001) but the scores at presentation and at first follow up were not significant (p = .29).

ALS is a devastating disease with relentless progressive course and death in almost all cases within span of few months to few years. As we now know that it is a multisystem disease, optimum care for patients with ALS is provided with a multidisciplinary environment where physiotherapists, occupational therapists, speech therapists, respiratory physicians, gastroenterologists, and social workers collaborate to guide symptomatic management throughout the course of disease (127).

The standard of care in our hospital is not protocol based but targeted according to individualized need. It includes inputs from physiotherapists & occupational therapists for improving muscle strength (endurance enhancing and breathing exercises) and rehabilitating them for activities of daily living (ADL). Speech therapists and ENT consultants help in improving speech and swallowing techniques. Depending on the case, Gastroenterologists or interventional radiologists help for PEG placement for appropriate nutrition. In cases with significant respiratory involvement, Pulmonologist are called for planning of NIV or tracheostomy.

Respiratory function and nutrition are crucial symptomatic concerns for patients with ALS, with respiratory failure being the main cause of death (128). Compared with patients managed in a general neurology clinic, patients managed in a specialized clinic had a better quality of life, possibly attributable to more effective use of resources, with benefits derived after a single visit (127).

Thus, this study aims at forming a strong base for developing a protocol for care of ALS patients which is multidisciplinary including psychologist as well. This includes planning of management that is affordable and easily available throughout India. As patient pays from his pocket, a state based specialized ALS clinic may not be available in near future. In such a scenario, only after studying the natural history, symptomatology, cost of investigations and cost of treatment – we can make an attempt to form a local-need-based cost-effective guidelines.

Table 18 Comparison between Retrospective and Prospective Data

	Retrospective study (2002-2012)	**Prospective study (2013)**
Number of cases	n = 286	n = 34
Mean (age in years)	48	49
Male: Female ratio	3 : 1	1.2 : 1
Duration of disease (mean)	16 months	22 months
Onset of disease	Bulbar – 25% Upper limb – 39% Lower limb – 34% Mixed – 02%	Bulbar – 23% Upper limb – 43% Lower limb – 34%
Rate of Progression	Rapid – 11% Intermediate – 62% Slow – 26.5%	Rapid – 06% Intermediate – 64% Slow – 30%
Initial **Spread**	Contralateral in 72% Ipsilateral in 15%	Ipsilateral in 45% Contralateral in 23.5%
Mean **FS-SS** duration	6 months	7 months
Risk Factors		
Hypertension	24%	20%
Diabetes	11%	06%
Smoking	27%	17.6%
Alcohol	12%	11.8%
Heavy metal	5.2%	8.8%
Organophosphorus	5.6%	11.8%
Native medication	28%	52.9%
Heavy Physical Activity	No data	26.4%
Diagnostic Category **El Escorial** –		
Clinically definite	31%	82%
Clinically Probable	57%	15%
Clinically Probable Lab Sup	09%	03%
Clinically Possible	03%	00
Diagnostic Category **Awaji Criteria**		
Clinically Definite	64%	91%
Clinically Probable	30%	09%
Clinically Possible	06%	00
Follow up at 3 months	21% (n = 59)	50% (n = 17)
ALSFRS-R worse	40 (68% of f/u pts)	12 (71% of f/u pts)
Died	10 (17% of f/u pts)	00
Follow up at 6 m or later	17% (n = 48)	38% (n = 13)
ALSFRS-R worse	36 (75% of f/u pts)	12 (93% of f/u pts)
Died	10 (21% of f/u pts)	00
Nonmotor manifestation		

Head Drop	5%	8%
Bladder	7%	5%
Extrapyramidal	5%	5%
Sensory symptoms	5%	2.9%
Abnormal SNAPs	15%	5.8%
Proximal Conduction block	8.3%	23%
Barium Swallow	n = 141 (49.3%)	n = 21 (62%)
Normal	46.8%	65%
Laryngeal Penetration	24%	12%
Abnormal Oral phase	29%	23%
PEG Insertion	2%	6%
Pulmonary **F**unction **T**est	n = 100 (35%)	n = 30 (88%)
Normal	13%	29%
Restrictive	47%	50%
Unable to do	29%	8%
Phrenic Nerve Conduction	n = 13 (4.5%)	n = 12 (35%)
Latency (mean)	6.43ms	7.43ms
Amplitude (mean)	0.8mv	1.25mv
MRI abnormal CST Signal	12%	23.5%
PET Scan done	05%	14.7%
Abnormal Brain metabolism	40% (2 out of 5)	6%
Diffusion Tensor Imaging	Not part of the study	n = 34
FA in ALS / Normative gr.		Significant correlation
FA along CST / ALSFRS-R		No Significant correlation
FA along CST / Cognition		Significant correlation
Cognitive Abnormalities	7% of cases. Dysexecutive and motor planning.	47% of cases. Deficits in Language, Executive functions, Behavior.

FS-SS – Duration between First symptom – second symptom
ALSFRS-R – ALS functional rating scale – revised
CST – Corticospinal tracts
FA – Fractional Anisotropy
PGIMS – PGI memory scale
FAB – Frontal Assessment Battery
ACE-R – Addenbrooke's Cognitive Examination - revised

CONCLUSION

1. The mean age of onset was 48 years which is almost a decade earlier than western data.
2. ALS is a group of disorder with a wide spectrum of clinical features and significant heterogeneity in presentation. The onset of the disease was in upper limb in 39%, lower limb in 34%, and bulbar region in 25%. The spread from first site to next is usually contiguous (for instance, from upper limbs to lower limbs and from lower limbs to upper limbs) and rarely, skip pattern of spread is also seen.
3. The rate of progression is best estimated by the duration between first symptom and second symptom. The rapidity of spread is most important prognostic factor.
4. The rate of progression was found to be significantly rapid in bulbar onset ALS. But there were bulbar onset cases which remain confined to bulbar region. Thus, serial follow up is very important.
5. ALS is now found to be a multisystem disease with involvement of bladder in 7%, extrapyramidal signs in 5%, sensory in 15% and cognition in at least 47% of cases.
6. About 50% of cases in our study had cognitive dysfunction. The main spheres affected are Language, Execution, Planning and in few cases behavior. There is a statistically significant correlation between cognitive dysfunction and DTI indices.
7. Several environmental and lifestyle factors were found that have not been studied well as yet, for example prior exposure to organophosphorus compounds and environmental toxins (seen in 5% of cases), as well as exposure to native

medications as an alternative therapy after the diagnosis. Around a third of our patients had history of exposure to native medications. There was a trend towards early onset, rapid progression and presence of myokymia on examination, in these cases.

8. There was a significant correlation between abnormal PFT and low amplitudes of phrenic nerve conduction.
9. Awaji-Shima Criteria, a modification of Revised El Escorial Criteria, increases yield of diagnosis (sensitivity increases), while preserving specificity.
10. ALSFRS-R scores are a good measure of the severity and stage of ALS. It tells the rate of progression in an individual when the scores are serially followed. But it doesn't include affective and cognitive dysfunction for which separate scales have to be used. It correlates with duration of disease, age of onset and rate of progression but not with DTI indices or cognitive scores.
11. In patients with amyotrophic lateral sclerosis there are significantly lower FA values along the corticospinal tract when compared to normative data starting from the subcortical white matter. This proves and thus establishes the upper motor neuron involvement in these patients.
12. There is no correlation between the DTI indices and the disease severity in amyotrophic lateral sclerosis in the present study. Diffusion tensor imaging is a useful modality in the objective estimation of UMN involvement and for serial monitoring of patients in ALS.

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Appendix-1

Christian Medical College, Vellore

Department of Neurology

PATIENT INFORMATION SHEET

A retrospective and prospective study of natural history, cognitive dysfunction and evaluation of upper motor neuron involvement in sporadic onset Amyotrophic Lateral Sclerosis (ALS) in patients treated at C.M.C. Hospital, Vellore.

Introduction

This study is being conducted by Department of Neurology, CMC Vellore. Amyotrophic Lateral Sclerosis is a common neurodegenerative illness. It causes weakness and wasting of various muscles of body over period of months to few years. It is heterogeneous condition and has many ways of presentation including different onset, different progression and involvement of different parts of body. The way it progresses also differs from person to person and depends on its onset. This disease usually involves motor weakness of various muscles of body but time and again, some non-motor symptoms and signs have been described. There is paucity of methodical research from India especially on the various non-motor manifestations of the disease like effect on one's cognition and sensory system. With newer diagnostic modalities some aspect of the disease can now be evaluated and quantified in detail, esp. upper motor neuron component of its pathology. The better we know about its pathology and pattern of progression, we can prognosticate and plan management more accurately and in a more holistic as well as individualized manner.

Methodology

After detailed assessment by the Neurology Department, you will be asked to undergo few tests including – Clinical (neuropsychological assessment), Electrophysiological (Nerve conduction and Electromyography, and Imaging (MRI Brain including Diffusion Tensor Imaging) for further studies for understanding the plausible cause of your disease and to rule out other diseases that resembles ALS. These tests may have to be repeated on your follow up visits.

Results

The result will be informed to the Neurologist who is primarily treating you. The result will not change your management plans as these results cannot be used immediately on patients.

Benefits

This study could throw light into the mechanisms of disease manifestation, its progression, and other aspect of natural history of the disease, ultimately helping physicians to form a better management plan for the patients.

Risks

The above mentioned tests are standard non-invasive tests done in our Institution and therefore there are no risks for those involved in the study.

Confidentiality

All information regarding the individuals participating in this study will be treated as strictly confidential. No information regarding your result will be disclosed to any person not connected with either your care or this study.

Volunteering for the study

Participation in this study is entirely voluntary. Your participation or non-participation will not affect any further treatment provided to you in this hospital.

Questions

If you have any doubts regarding the study you may clarify them now or contact either of the following:

Dr Mathew Alexander Neurology Department Phone: 0416-2282018

Dr Varun Kataria Neurology Department Phone: 0416-2282018

Dr Sanjit Aaron, Neurology Phone: 0416- 2282018

Appendix-2

CONSENT FORM

I, ……. father / mother of …….. (Hospital number ……) have been explained the details of the study as recorded in the Patient Information Form. I agree to participate in this study. All of my questions regarding the study have been answered satisfactorily.

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights

I understand that my identity will not be revealed in any information released to third parties or published

1. Signature / thumb impression of participant's parent…….

Name: ……. Date: …….

2. Signature / thumb impression of witness……..

Name: …….. Date: …….

3. Investigator's signature …… Date: ……..

Appendix – 3

THE ALS FUNCTIONAL RATING SCALE – REVISED: (ALSFRS – R)

Measure	Finding	Points
Speech	Normal	4
	Detectable speech disturbance	3
	intelligible with repeating	2
	speech combined with non vocal communications	1
	loss of useful speech	0
Salivation	Normal	4
	slight but definite excess of saliva in mouth;	3
	may have nighttime drooling	2
	Moderately excessive saliva: may have minimal drooling	1
	marked excess of saliva with some drooling	0
	marked drooling; requires constant tissue or handkerchief	
Swallowing	Normal	4
	early eating problems; occasional choking	3
	dietary consistency changes	2
	needs supplemental tube feedings	1
	nothing by mouth (NPO); exclusively parenteral or enteral feeding	0
Hand writing	Normal	4
	slow or sloppy; all words are legible	3
	not all words are legible	2
	able to grasp pen but unable to write	1
	unable to grip pen	0
Cutting Food and handling utensils	no gastrostomy/normal	4
	no gastrostomy: somewhat slow and clumsy but no help required	3
	no gastrostomy: can cut most foods although clumsy and slow; no help needed	2
	no gastrostomy: food must be cut by someone but can still feed slowly	1
	no gastrostomy: needs to be fed	0
	with gastrostomy: normal	4
	with gastrostomy: clumsy but able to perform all manipulations independently	3
	with gastrostomy: some help needed with closures and fasteners	2
	with gastrostomy: provides minimal assistance to caregiver	1

	with gastrostomy: unable to perform any aspect of task	0
Dressing and Hygiene	Normal	4
	independent and complete self-care with effort or decreased efficiency	3
	intermittent assistance or substitute methods	2
	needs attendant for self-care	1
	total dependence	0
Turning in Bed and Adjusting bed Clothes	Normal	4
	somewhat slow and clumsy but no help needed	3
	can turn alone or adjust sheets but with great difficulty	2
	can initiate but not turn or adjust sheets alone	1
	helpless	0
Walking	Normal	4
	early ambulation difficulties	3
	walks with assistance	2
	Non ambulatory functional movement only	1
	no purposeful leg movement	0
Climbing stairs	Normal	4
	slow	3
	Mild unsteadiness or fatigue	2
	Needs assistance	1
	Cannot do	0
Breathing	Normal	4
	Shortness of breath with minimal exertion (walking talking etc.)	3
	shortness of breath at rest	2
	intermittent (e.g. nocturnal) ventilatory assistance required	1
	ventilator dependent	0
Orthopnea	No change	4
	Occasional shortness of breath, does not routinely use more than two pillows	3
	Require more than 2 pillows to sleep value	2
	Can only sleep sitting up	1
	Require the use of respiratory support (BiPAP®) to sleep	0
Respiratory Insufficiency	No respiratory support value	4
	Intermittent use of BiPAP	3
	Continuous use of BiPAP at night	2
	Continuous use of BiPAP day and night	1
	Invasive mechanical ventilation	0

Appendix-4

Frontal Assessment Battery

1. Similarities (conceptualization)

"In what way are they alike?"

- A banana and an orange

(In the event of total failure: "they are not alike" or partial failure: "both have peel," help the patient by saying: "both a banana and an orange are fruit"; but credit 0 for the item; do not help the patient for the two following items)

- A table and a chair
- A tulip, a rose and a daisy

Score (only category responses [fruits, furniture, flowers] are considered correct)

Three correct: 3 Two correct: 2 One correct: 1 None correct: 0

2. Lexical fluency (mental flexibility)

"Say as many words as you can beginning with the letter 'S,' any words except surnames or proper nouns."

If the patient gives no response during the first 5 seconds, say: "for instance, snake." If the patient pauses 10 seconds, stimulate him by saying: "any word beginning with the letter 'S.' The time allowed is 60 seconds.

Score (word repetitions or variations [shoe, shoemaker], surnames, or proper nouns are not counted as correct responses)

> 9 words: 3 6 -9 words: 2 3 -5 words: 1 < 3 words: 0

3. Motor series "Luria" test (programming)

"Look carefully at what I'm doing."

The examiner, seated in front of the patient, performs alone three times with his left hand the series of "fist–edge–palm."

"Now, with your right hand do the same series, first with me, then alone."

The examiner performs the series three times with the patient, and then says to him/her:

“Now, do it on your own.”

Score

Patient performs six correct consecutive series alone: 3

Patient performs at least three correct consecutive series alone: 2

Patient fails alone, but performs three correct consecutive series with the examiner: 1

Patient can’t perform three correct consecutive series even with the examiner: 0

4. Conflicting instructions (sensitivity to interference)

“Tap twice when I tap once.”

To ensure that the patient has understood the instruction, a series of 3 trials is run: 1-1-1.

“Tap once when I tap twice.”

To ensure that patient has understood the instruction, a series of 3 trials is run: 2-2-2.

The examiner then performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score No errors: 3 1 -2 errors: 2 > 2 errors: 1

Patient taps like the examiner at least four consecutive times: 0

5. Go–No Go (inhibitory control)

“Tap once when I tap once.”

To ensure that patient has understood the instruction, a series of 3 trials is run: 1-1-1.

“Do not tap when I tap twice.”

To ensure that patient has understood the instruction, a series of 3 trials is run: 2-2-2.

The examiner then performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score No errors: 3 1 -2 errors: 2 > 2 errors: 1

Patient taps like the examiner at least four consecutive times: 0

6. Prehension behavior (environmental autonomy)

“Do not take my hands.”

The examiner is seated in front of the patient. Place the patient’s hands palm up on his knees. Without saying anything or looking at the patient, the examiner brings his own hands close to the patient’s hands and touches the palms of both the patient’s hands, to see if he will spontaneously take them. If the patient takes the examiner’s hands, try again after asking the patient: “Now, do not take my hands.”

Score

Patient does not take the examiner’s hands: 3

Patient hesitates and asks what he/she has to do: 2

Patient takes the hands without hesitation: 1

Patient takes the examiner’s hand even after he/she has been told not to do so: 0

Interpreting results

A cut off score of 12 on the FAB has a sensitivity of 77% and specificity of 87% in differentiating between frontal dysexecutive type dementias and DAT

References

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Appendix- 5

Pro forma for Postal Questionnaire

Dear Mr._____ (name of patient)

Greetings from Department of Neurological Sciences:

We are planning a study in Department of Neurological Science, CMC Vellore. The aim is to study various aspects of Motor Neuron Disease (also known as Amyotrophic Lateral Sclerosis). As you already are aware, this disease affects the motor nerves of the body causing weakness of various muscles of body. Unfortunately, there's no cure for this debilitating disease. Thus, the better the understanding of the onset, progression, spread and outcome of this illness, the better will be management plan as well as more accurately one can predict and prognosticate its manifestations. For the same purpose, it would be highly beneficial if you can come for follow-up & assessment. I hope you will enthusiastically participate.

In case you are not able to come to C.M.C. Hospital, Vellore, you can participate by filling the following questionnaire and sending it to "Department of Neurology, C.M.C. Hospital, Vellore, 632004." The details and identity of each participant will be kept confidential.

In case of unfortunate circumstances of demise of the patient, the immediate family members are requested to fill the details. This would not only help in better understanding of the disease, but also help us in proper individualized treatment & care of patients who are still suffering or will come to us for treatment.

PRO FORMA

DEMOGRAPHY:

1. Name of Patient:
2. Age:
3. History of active participation in contact/field sports previously:
4. Occupation:
5. Family history:
    - Any family member suffering from similar illness? – if yes, please provide the detail
    - Any relative is suffering from other neurodegenerative illness?
6. Last visit to C.M.C. Hospital, Vellore:
7. Last visit to other physicians or neurologists (Please provide a scanned copy or photocopy of the prescription/clinical notes of your last medical minutes.

CLINICALS:

8. Handedness:
9. Number of months / years into illness:
10. At the onset of the disease, what was the chief problem -
    - Hand weakness
    - Leg weakness
    - Voice change
    - Difficulty in speaking and swallowing

11. Medications: - Please state the number of months/years of each treatment taken and brief about their effect on your disease
    - Riluzole:
    - Steroids:
    - Immunomodulation/ Cyclophosphamide –
    - Any other –

12. Outcome: Current Activities of daily living –

(1) Speech: Normal: Decreased clarity: Severe problem: No useful speech:	(2) Salivation: Normal Increased: Marked drooling:
(3) Swallowing: No problem: Mild difficulty/occasional choking: Effortful and change in consistency	(4) Handwriting: Normal: Slow and sloppy: Able to grasp pen but not able to

of food: Tube feeding:	write: Unable to grasp pen:
(5) Cutting food and handling utensils - normal: Slow and clumsy: Food to be cut by somebody else but can feed himself: Has to be fed by someone:	(6) Dressing and hygiene – Normal: Independent but requires more effort: Requires occasional assistance: Dependent on others:
(7) Turning in bed and adjusting bed clothes - Normal: Slow and clumsy: Requires help; Dependent on others:	(8) Walking – Normal: Mild difficulty: Requires assistance: Nonambulant:
(9) Climbing stairs – Unaided: Slow and mild difficulty: Needs assistance: Cannot walk on stairs:	(10) Breathing – Normal: Shortness of breath on exertion: Shortness of breath on lying down (requiring more than one pillow): Requires ventilator assistance (CPAP/BiPAP):

Contact Details:

Dr. Varun Kataria

Department of Neurological Sciences

C.M.C. Hospital, Vellore

Tamil Nadu, 632004

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: 09488343346
Email: varunkataria@rediffmail.com
: neurology@cmcvellore.ac.in

Appendix- 6

PROFORMA

DEMOGRAPHY:

13. Name:
14. Age:
15. Address:
16. Occupation:
17. Life style:
    Sports and Manual Activity:
    Alcohol Consumption:
    Smoking / Tobacco:
18. Diet:
19. Educational background:
20. Family history:

CLINICALS:

21. Age at onset:
22. Number of months / years into illness:
23. Course – Upper limb onset – distal/proximal
    - Lower limb onset – distal/proximal
    - Bulbar onset – voice/swallowing/breathing
24. Motor system examination – MRC grading of muscle power**, Deep tendon reflexes, clonus.
25. Sensory examination:
26. Fasciculations:

27. **Clinical spectrum:**

    Cognition – MMSE, Frontal lobe battery*, Neary Criteria**

    Extrapyramidal features:

    Cranial nerves:

    Tone & spasticity: Generalized / lower limbs only

    Pattern of muscle wasting – distal/proximal

    Sensory system – clinical, ENMG (SNAPs)

    Autonomic system – bedside tests, SSR

28. ENMG: -
29. MRI C-spine, Brain:
30. PET Scan:
31. DTI Scan and indices:

EL ESCORIAL CRITERIA:

AWAJI CRITERIA:

32. Medications: -
    - Riluzole
    - Steroids
    - Immunomodulation

33. Outcome: ADLs / dependence / current occupation **(ALSFRS-R)***

** Given in Appendix3, 4*

*** Given Below*

MRC Motor Power Grading

Neck Flexion Extension		
Trunk		
Shoulder Abduction Adduction Flexion Extension		
Arm Flexion Extension		
Wrist Flexion Extension		
Hand Grip		
Small muscles of hand Median Ulnar		
Hip Flexion Extension Abduction Adduction		
Knee Flexion Extension		
Foot Dorsiflexion Plantarflexion Inversion Eversion		
EHL / EDB		

Consensus criteria for FTD

I.	**Core diagnostic features**	A. Insidious onset and gradual progression B. Early decline in social interpersonal conduct C. Early impairment in regulation of personal conduct D. Early emotional blunting E. Early loss of insight
II.	**Supportive diagnostic features**	**A. Behavioral disorder** 1. Decline in personal hygiene and grooming 2. Mental rigidity and inflexibility 3. Distractibility and impersistence 4. Hyperorality and dietary changes 5. Perseverative and stereotyped behavior 6. Utilization behavior **B. Speech and language** 1. Altered speech output a. Aspontaneity and economy of speech b. Pressure of speech 2. Stereotypy of speech 3. Echolalia 4. Perseveration

	5. Mutism **C. Physical signs** 1. Primitive reflexes 2. Incontinence 3. Akinesia, rigidity, and tremor 4. Low and labile blood pressure
D. Investigations 1. Neuropsychology: impairment on frontal lobe tests without severe amnesia, aphasia, or perceptuospatial disorder 2. Electroencephalography: normal on conventional EEG despite clinically evident dementia 3. Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality	

- *Consensus criteria for FTD (based on Neary, 1998)*

Appendix - 7

COGNITIVE SCORES:

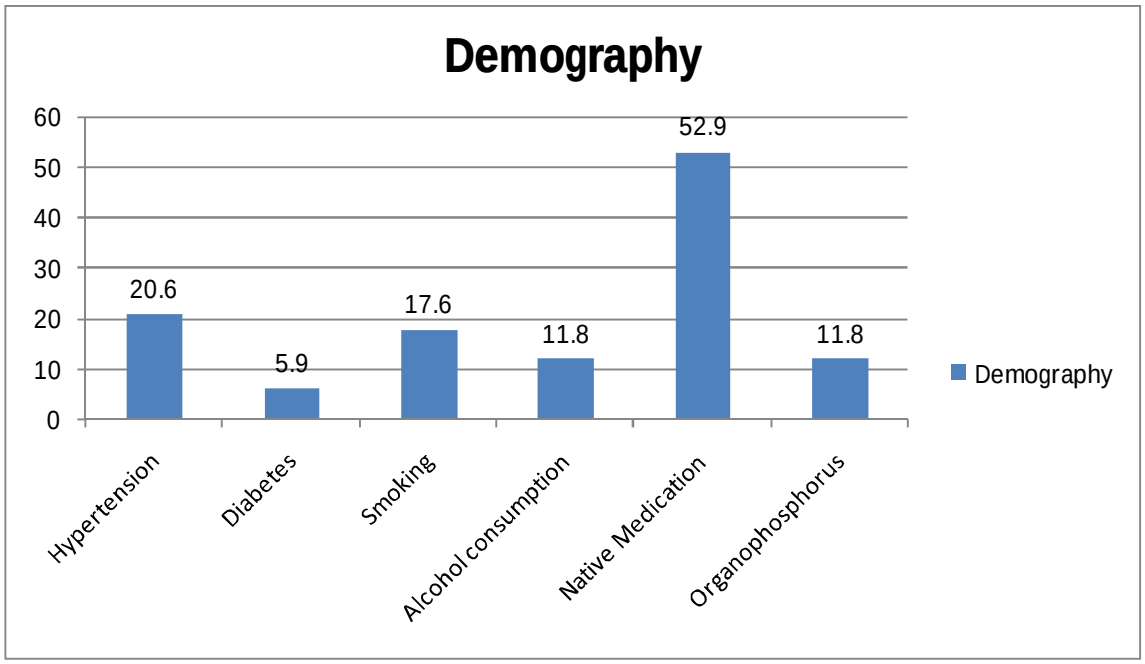
SCALE	NORMATIVE	ALS GROUP
P.G.I.M.S. (PGI Memory Scale)		
Remote Memory	5.75 ± 0.52	
Recent Memory	4.9 ± 0.31	
Mental Balance	7.83 ± 1.66	
Attention & Concentration	9.77 ± 1.74	
Verbal retention for similar pairs	4.53 ± 0.73	
Verbal retention for dissimilar pairs	12.33 ± 2.44	
Visual retention	10.33 ± 2.50	
Visual recognition	8.87 ± 1.25	
Frontal Assessment Battery (FAB)		
Conceptualization	3	
Mental Flexibility	3	
Motor Programming	3	
Sensitivity to interference	3	
Inhibitory Control	3	
Environmental Autonomy	3	
NIMHANS Battery for Adults (2004)		
Focused Attention (Color Trails Test)	> 15th percentile	
Verbal Learning & Memory (AVLT) – Recall &	> 15th percentile	

Recognition trials		
Immediate Recall	> 15th percentile	
Delayed Recall	> 15th percentile	
Long Term Percent Retention (LTPR)	> 15th percentile	
Visual Learning & Memory – Complex Figure test	> 15th percentile	
Copy	> 15th percentile	
Immediate recall	> 15th percentile	
Delayed recall	> 15th percentile	
Addenbrooke's Cognitive Examination – Revised (ACE-R)		
Attention and orientation	Normal	
Memory	Normal	
Fluency	Normal	
Language	Normal	
Visuo-spatial	Normal	
TOTAL		

Appendix - 8

Demography- Normative and Disease group

	Normative Group	**ALS Group**
Number	25	34
Age	45 ± 12 years	49 ± 15 years
Sex	60% male, 40% female	55% male, 45% female
Education		
School	10	8
College	7	12
Post graduate	8	14
Risk Factors		
Diabetes	4	2
Hypertension	10	7
Smoking	4	6
Alcohol	3	4
Neurological Problem	Headache, vertigo, Nonspecific complaints	
Neurological Examination including cognition	Normal	
MRI	18 – normal 07 – nonspecific white matter changes	


Demography
60
50
40
30
20
10
0
20.6
5.9
17.6
11.8
52.9
11.8
Hypertension
Diabetes
Smoking
Alcohol consumption
Native Medication
Organophosphorus
Demography

Appendix – 9

The diagnosis of Amyotrophic Lateral Sclerosis (ALS) requires

A. The presence of:

(A: 1) evidence of lower motor neuron (LMN) degeneration by clinical electrophysiological or neuropathologic examination,

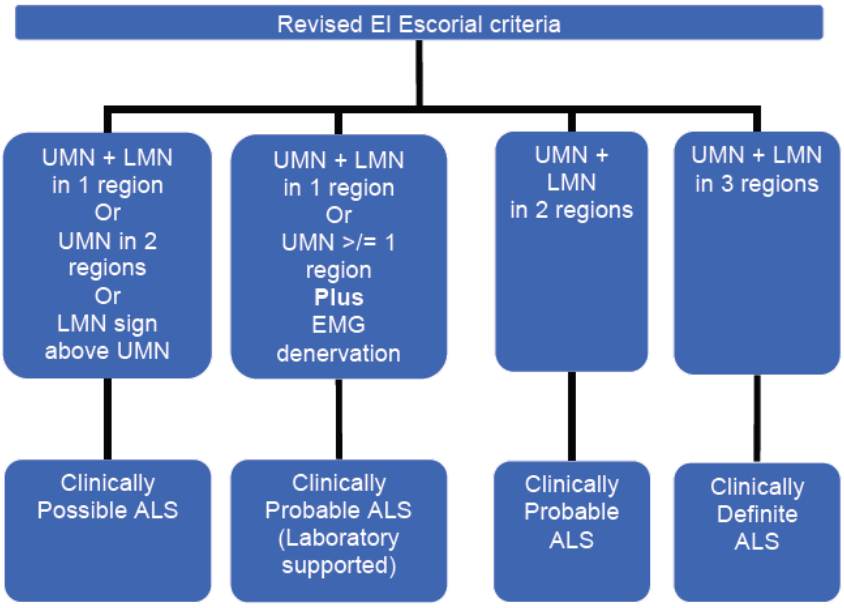
(A: 2) evidence of upper motor neuron (UMN) degeneration by clinical examination, and

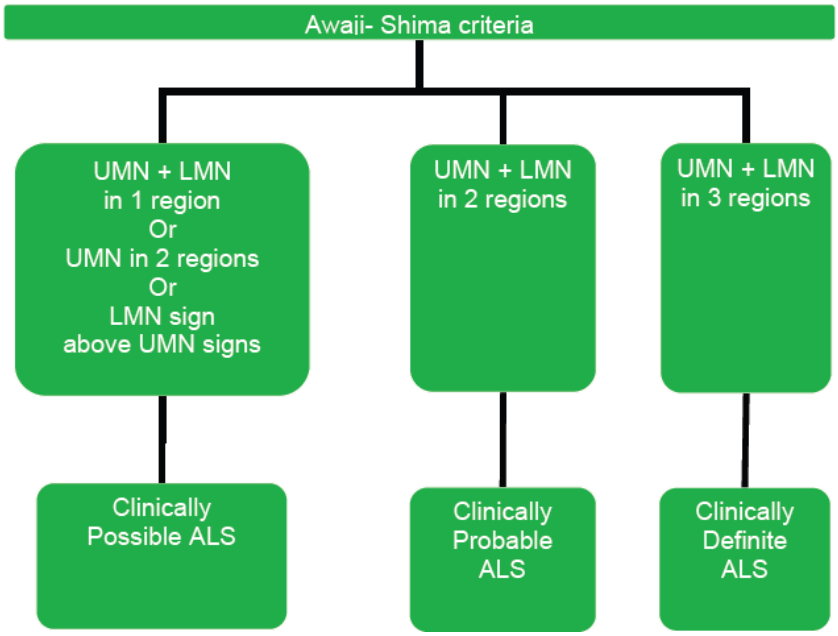
(A: 3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination, together with

B. The absence of:

(B: 1) electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and

(B: 2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.





An evaluation of neurophysiological criteria used in the diagnosis of Motor Neuron Disease
Douglass CP, Kandler RH, Shaw PJ and McDermott CJ
Journal of Neurology, Neurosurgery & Psychiatry 81, 6 (2010) 646

Table 4

Summary of the Revised El Escorial Criteria and Awaji Criteria for ALS **Diagnosis: Differences between Awaji-Shima Consensus Recommendations and the Revised El Escorial Criteria (Airlie-House 1998)**	
The diagnosis of ALS requires:	
Principles of the Revised El Escorial Criteria	Principles of the Awaji Shima Consensus Recommendations
Evidence of LMN loss (Reduced interferential pattern on full contraction and increased firing rate)	Evidence of LMN loss (Reduced interferential pattern on full contraction and increased firing rate)
Evidence of re-innervation (motor units of large amplitude and longer duration)	Evidence of re-innervation (motor units of large amplitude and longer duration)
Fibrillations and sharp waves	Fibrillations and sharp waves or fasciculation potentials
No. of muscles affected by Region: Cervical and Lumbosacral region: minimum of 2 muscle innervated by different roots and nerves Bulbar and Thoracic region: a minimum of 1 muscle	
Diagnostic Classification:	
Clinically definite ALS is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least 2 spinal regions or the presence of LMN and UMN signs in 3 spinal regions.	
Clinically probable ALS is defined on clinical or electrophysiological evidence by LMN and UMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN signs. The revised El Escorial Criteria have an additional category "Probable ALS–Laboratory Supported," which is defined when clinical signs of UMN and LMN dysfunction are found in only 1 region but electrophysiological signs of LMN loss are observed in >2 regions.	
Clinically possible ALS is defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only 1 region or UMN signs are found alone in >2 regions or LMN signs are found rostral to UMN signs.	

Appendix 10

DTI indices:

Normative group:

ROI	FA (Mean ± SD)	MD (Mean ± SD) (10 – 3 mm2/sec)
Genu	0.81 ± 0.05	0.97 ± 0.07
Splenium	0.82 ± 0.04	0.93 ± 0.08
Right centrum semiovale (normal appearing white matter) *	0.47 ± 0.04	0.92 ± 0.08
Left PLIC **	0.69 ± 0.05	0.88 ± 0.07
Right anterior periventricular white matter	0.49 ± 0.05	0.93 ± 0.08
Left anterior periventricular white matter	0.5 ± 0.05	0.88 ± 0.08
Right posterior periventricular white matter	0.55 ± 0.06	0.95 ±0.07
Left posterior periventricular white matter	0.55 ± 0.05	0.94 ± 0.07
Right Cerebral peduncle	0.71 ± 0.07	0.92 ± 0.07
Left Cerebral peduncle	0.74 ± 0.05	0.94 ± 0.09
Right pyramid	0.58 ± 0.06	0.88 ± 0.09
Left pyramid	0.58 ± 0.06	0.88 ± 0.10
Right subcortex (at the region of the CST ***)	0.58 ± 0.06	0.91 ± 0.10
Left subcortex (at the region of the CST ***)	0.58 ± 0.05	0.89 ± 0.09
Right frontal lobe	0.49 ± 0.07	0.95 ± 0.08
Left frontal lobe	0.49 ± 0.08	0.90 ± 0.07

Appendix – 11

Key for the Master Chart
Retrospective Group, n = 286
Prospective Group, n = 34

1. Sex - 0 = male 1 = female	2. Onset – 0 = Bulbar 1 = Upper limb 2 = Lower limb 3 = Mixed
3. Progression1 – 0 = UL-LL-Bulb 1 = LL-UL-Bulb 2 = Bulb-UL-LL 3 = LL-Bulb-UL 4 = Bulb-LL-UL 5 = UL-Bulb-LL	4. Progression2 – 0 = Nonprogressive 1 = Rapid 2 = Intermediate 3 = Slow
5. Education – 0 = illiterate 1 = Primary School 2 = Secondary School 3 = College 4 = Graduate	6. Hypertension 0 = Absent; 1 = Present 7. Diabetes 0 = Absent; 1 = Present 8. Smoking 0 = Absent; 1 = Present 9. Alcohol 0 = Absent; 1 = Present 10. IHD 0 = Absent; 1 = Present 11. Native Medication 0 = Absent; 1 = Present 12. Organophosphorus 0 = Absent; 1 = Present 13. Toxins 0 = Absent; 1 = Present 14. Obesity 0 = Absent; 1 = Present 15. Sports 0 = Absent; 1 = Present
16. CVS examination 0 = Normal; 1 = Abnormal	17. Respiratory system 0 = Normal; 1 = Abnormal 18. Abdomen 0 = Normal; 1 = Abnormal
19. Weight Loss – 0 = <5kg 1 = 5-10kgs 2 = >10kgs	20. Neck Height Ratio – 0 = normal; 1 = low 21. Eye movement – 0 = normal; 1 = Abnormal 22. Facial Nerve - 0 = normal; 1 = Abnormal 23. Head drop - 0 = Absent; 1 = Present
24. FAB Frontal assessment battery – 0 = Not done 1 = Normal 2 = Abnormal Similarities 3 = Abnormal Lexical Fluency	25. Trigeminal Nerve 0 = Normal 1 = Motor Weakness, esp. jaw 2 = Abnormal facial sensation 3 = Brisk jaw jerk 26. Palatal Examination 0 = normal 1 = gag sluggish

4 = Abnormal Luria's test 5 = Abnormal Go-no-go 6 = Abnormal Conflicting instruct 7 = Environmental Autonomy 8 = 2 or > 2 categories abnormal	2 = gag exaggerated
27. Wasting – 0 = in distal upper limbs only 1 = in prox and distal ULs 2 = in lower limbs 3 = UL and LLs 4 = No wasting 5 = over UL and tongue	28. Spasticity 0 = Normal 1 = spasticity in LLs 2 = in ULs and LLs 3 = Hypotonia 29. Pattern of weakness 0 = distal to proximal 1 = proximal to distal 2 = simultaneously
26. Deep tendon Reflex 0 = normal 1 = brisk 2 = sluggish	27. Plantar reflex, right and left 0 = flexor 1 = extensor
28. Sensory system 0 = normal 1 = abnormal	29. Cerebellar signs 0 = absent 1 = present
30. Romberg's sign 0 = absent 1 = present	31. Gait 0 = normal 1 = assisted 2 = spastic 3 = non ambulant
32. FascicsH – History of fasciculation 0 = Absent 1 = present	33. FascicsE – Fasciculations on Examination 0 = Absent 1 = Present
34. SNAP – Sensory nerve action potential 0 = normal 1 = abnormal	35. Biopsy of nerve/ muscle 0 = not done 1 = normal 2 = Vasculitis like 3 = nonspecific inflammation

36. ActDener – Active denervation according to El Escorial criteria 0 = absent / insufficient data 1 = 1 region only 2 = 2 regions 3 = 3 or >3 regions	37. ChrDener – Chronic denervation 0 = absent / insufficient data 1 = 1 region only 2 = 2 regions 3 = 3 or >3 regions
38. Elesco – Diagnostic Category according to El Escorial criteria 0 = Clinically Definite 1 = Clinically Probable 2 = Clinically Probable Lab supported 3 = Clinically Possible	39. ActDener1 – Active denervation according to Awaji Criteria 0 = absent / insufficient data 1 = 1 region only 2 = 2 regions 3 = 3 or >3 regions
40. Awaji Criteria Diagnostic category 0 = Clinically Definite 1 = Clinically Probable 2 = Clinically Possible	41. ChrDener1 – Chronic denervation 0 = absent / insufficient data 1 = 1 region only 2 = 2 regions 3 = 3 or >3 regions
42. Proxconduc – Root stimulation / proximal conductions 0 = done 1 = not done	43. Condbloc – Conduction block 0 = absent 1 = Present at entrapment sites 2 = present apart from entrapment sites 3 = present on root stimulation
44. Spirometry 0 = Normal 1 = Restrictive 2 = Obstructive 3 = Not able to perform 4 = not done	45. Barium – Barium swallow 0 = not done 1 = normal 2 = Aspiration/Laryngeal penetration 3 = Abnormal oral phase only

46. Immune – Autoimmune markers 0 = not available 1 = negative 2 = positive	47. Toxscrn – Toxin screening in blood/urine 0 = not available 1 = negative 2 = positive
48. PEG – Percutaneous Endoscopic Gastrostomy 0 = Not Required 1 = Required but not done 2 = Done 3 = Not done – reason unknown	49. MRI1 – MRI cervical spine 0 = Not available 1 = Normal (including cervical disc changes but no significant root or cord compression) 2 = Abnormal cervical cord signals
50. PET – Whole body PET CT Scan 0 = not done 1 = normal 2 = Abnormal (malignancy, infections, inflammation) 3 = Abnormal Brain PET	51. MRI2 – MRI Brain 0 = not available 1 = normal 2 = Abnormal (old infarcts, nonsignificant small vessel disease) 3 = Symmetrical Hyperintensities along cortico-spinal tracts
52. Therapy – Therapeutic trial 0 = symptomatic 1 = Riluzole 2 = Riluzole + Immunomodulation	53. Response – Response to therapy 0 = Present 1 = No response 2 = lost to follow up
54. Outcome – Outcome at discharge 0 = alive 1 = died	55. Followup1 & Followup2 – Follow up at 3 months and at 6 months or later 0 = No follow up 1 = ALSFRS-R improving 2 = ALSFRS-R static 3 = ALSFRS-R worsening 4 = died
56. Bladder symptoms 57. Myokymia 0 = Absent; 1 = Present	58. Extrapyramidal symptoms or signs 0 = Absent 1 = Present

Name	HospNo	Adress	Age	Sex	maritalstat	Ioccpt	education	Htn	Smoking	IHD	PVD	RenalFail
Kakali Khanra	355738F	W.B.	35	2	1	1	0.00	0	0	0	0	0
Annamma Varghese	285815f	Kerela	65	2	1	0	4.00	0	0	0	0	0
Ranen Dutta	597029b	W.B.	49	1	1	4	4.00	0	0	0	0	0
Yazmin	152226F	Srilanka	56	2	1	4	4.00	1	0	0	0	0
Elizabeth Kunnel.SR	207100D	Vellore	66	2	0	5	3.00	1	0	0	0	0
Saraswati Halder	499545D	W.B.	49	2	1	0	3.00	0	0	0	0	0
Madhay Biswas	053832f	W.B.	44	1	1	3	1.00	0	0	0	0	0
Radha Devi Lath	135690F	Bihar	55	2	1	0	1.00	1	0	0	0	0
Imtiyaz Samim Mahmud	084538F	W.B.	48	1	1	4	3.00	0	1	0	0	0
Arjun Prasad Yadav	029233f	Bihar	45	1	1	5	3.00	1	0	0	0	0
Nilam Devi	210762F	Jharkhand	49	2	1	0	1.00	0	0	0	0	0
Jibraiel Ansari	225584F	Jharkhand	40	1	1	3	1.00	0	0	0	0	0
Sankar Kamila	205825F	W.B.	51	1	1	3	1.00	0	0	0	0	0
Budheswar Kulley	201587F	W.B.	35	1	1	1	0.00	0	0	0	0	0
Bhubaneswari Adhikari	286178F	W.B.	49	2	1	0	2.00	0	0	0	0	0
Mukti Rani Sarkar	231994F	W.B.	47	2	1	0	2.00	1	0	0	0	0
George Fenn T.B.	117703F	Kerela	64	1	1	4	4.00	1	0	0	0	0
Subas Sardar	131357F	W.B.	40	1	1	2	2.00	0	1	0	0	0
Bholanath jana	348509F	W.B.	37	1	1	1	1.00	0	0	0	0	0
Kajaal Rani Barik	153137F	W.B.	41	2	1	0	2.00	0	0	0	0	0
Dipali Dey Dutta	287904F	W.B.	38	2	1	0	2.00	0	0	0	0	0
Kishor Ray	005026F	Bihar	55	1	1	4	3.00	0	1	0	0	0
Md. Zahangir Alam Ali	906463D	Bangladesh	47	1	1	4	3.00	0	1	0	0	0
Bala Anki Reddy B.	127433F	A.P.	59	1	1	5	4.00	0	0	0	0	0
Tamilazakan B	205788F	T.N.	42	1	1	4	4.00	0	0	0	0	0
Anil Kumar Gpta	315731F	W.B.	53	1	1	4	4.00	0	1	0	0	0
Kochu Janaki M.E.	302602F	Kerela	62	2	1	5	4.00	0	0	0	0	0
Jessy Thomas	285582F	Kerela	48	2	1	5	4.00	0	0	0	0	0
Justice Abdul Gafoor	139520F	Kerela	67	1	1	5	4.00	1	0	1	0	0
Bernice Gregory	382853F	Kerela	60	2	1	0	4.00	0	0	0	0	0
Shyamapada Pal	391721F	W.B.	53	1	1	4	4.00	0	0	0	0	0
Ravi Shankar	382388F	Bihar	36	1	1	2	2.00	0	1	0	0	0
Raj Singh	182078F	Assam	48	2	1	5	4.00	0	0	0	0	0
Palaniyandi	099530D	T.N.	59	1	1	5	4.00	0	0	0	0	0

NativeMed	Diabet	Alcohol	Obesity	OP	Vegetarian	Toxin	Hiphysical	Familyhistory	WeightLoss	Neckheightratio	CVS	RS
0	0	0	0	1	0	0	1.00	0.00	1	1.0	0	0
1	0	0	1	0	0	0	0.00	0.00	2	1.0	0	0
1	0	0	0	0	0	0	0.00	0.00	1	1.0	0	0
0	0	0	0	0	0	0	1.00	0.00	1	1.0	0	0
0	1	0	0	0	0	0	0.00	0.00	1	1.0	0	0
1	0	0	0	0	0	0	0.00	0.00	2	1.0	0	0
1	0	0	0	1	0	1	1.00	0.00	1	1.0	0	0
1	0	0	0	0	0	0	0.00	0.00	1	1.0	0	0
0	0	0	0	0	0	0	0.00	0.00	1	1.0	0	0
0	0	0	0	0	0	0	0.00	0.00	2	1.0	0	0
0	0	0	0	0	0	0	0.00	0.00	1	1.0	0	0
1	0	0	0	1	0	0	1.00	0.00	1	1.0	0	0
1	0	0	0	1	0	0	1.00	0.00	1	1.0	0	0
0	0	0	0	0	0	0	1.00	0.00	1	1.0	0	0
0	0	0	0	0	0	0	0.00	0.00	2	1.0	0	0
1	1	0	0	0	0	0	0.00	0.00	1	1.0	0	0
0	0	1	0	0	0	0	0.00	0.00	1	1.0	0	0
1	0	1	0	0	0	0	0.00	0.00	1	1.0	0	0
1	0	1	0	0	0	0	1.00	0.00	2	1.0	0	0
0	0	0	0	0	0	0	0.00	0.00	1	1.0	0	0
0	0	0	0	0	0	0	0.00	0.00	1	1.0	0	0
1	0	0	0	0	0	1	0.00	0.00	1	1.0	0	0
1	0	0	0	0	0	0	0.00	0.00	2	1.0	0	0
1	0	0	0	0	0	0	0.00	0.00	1	1.0	0	0
1	0	0	0	0	0	0	0.00	0.00	2	1.0	0	0
0	0	0	0	0	1	0	0.00	0.00	2	1.0	0	0
1	0	0	0	0	0	1	0.00	0.00	1	1.0	0	0
1	0	0	0	0	0	0	0.00	0.00	1	1.0	0	0
0	0	0	0	0	0	0	1.00	0.00	2	1.0	1	0
0	0	0	0	0	0	0	0.00	0.00	1	1.0	0	0
1	0	0	0	0	0	0	0.00	0.00	2	1.0	0	0
0	0	1	0	0	0	0	0.00	0.00	1	1.0	0	0
0	0	0	0	0	0	0	1.00	0.00	1	1.0	0	0
1	0	0	0	0	0	0	0.00	0.00	2	1.0	0	0

ABD	MMSE	Olfact	Vision	Eyemov	trig	Facial	vestc	palate	wasting	Tone	Nflx	next
0	26	0	0	1	0	0	0	2	0	2	1	0
0	29	0	0	0	1	1	0	2	3	1	1	2
0	29	0	0	0	3	1	0	1	1	0	0	1
0	27	0	0	1	3	1	0	2	3	2	1	0
0	28	0	0	0	1	1	0	0	0	1	1	0
0	27	0	0	1	1	1	0	1	1	1	1	2
0	26	0	0	0	3	1	0	2	3	1	0	0
0	27	0	0	0	3	1	0	2	0	2	1	1
0	28	0	0	0	0	0	0	0	3	2	1	0
0	29	0	0	0	1	0	0	1	0	1	1	1
0	30	0	0	0	3	1	0	1	4	0	0	0
0	28	0	0	0	0	0	0	0	1	1	0	0
0	28	0	0	0	0	0	0	0	3	1	0	0
0	27	0	0	0	0	1	0	1	3	0	1	1
0	30	0	0	0	1	1	0	2	0	1	1	1
0	30	0	0	0	0	1	0	1	5	1	1	1
0	30	0	0	0	3	0	0	1	5	0	1	1
0	29	0	0	1	1	1	0	1	3	1	1	1
0	26	0	0	1	3	1	0	2	3	2	1	2
0	29	0	0	0	1	1	0	1	3	1	1	1
0	29	0	0	1	1	1	0	2	5	0	1	0
0	30	0	0	0	3	1	0	2	5	1	1	1
0	29	0	0	0	3	0	0	0	5	1	1	0
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0	30	0	0	1	3	1	0	1	3	1	0	0
0	21	0	0	0	3	1	0	2	3	1	0	0
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0	30	0	0	0	0	0	0	0	3	3	1	1
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0	29	0	0	0	3	1	0	2	3	2	0	0
0	29	0	0	1	3	0	0	2	5	2	1	0
0	27	0	0	0	1	1	0	2	3	3	1	2

trunk	ShabdR	ShabdL	ShaddR	ShaddL	ShflxR	Shflx	ShextR	ShextL	ElbflxR	ElbflxL	ElbextR	ElbextL
1	5.00	5.00	5.00	5.00	5.00	5	4.00	4	5.00	5	4.00	4
1	4.00	2.00	4.00	2.00	4.00	2	4.00	2	4.00	2	4.00	2
1	4.00	5.00	4.00	5.00	4.00	5	4.00	5	4.00	5	4.00	5
1	4.00	4.00	4.00	3.00	4.00	4	4.00	3	4.00	4	4.00	4
1	5.00	5.00	5.00	5.00	5.00	5	5.00	5	5.00	5	5.00	5
1	3.00	3.00	3.00	3.00	3.00	3	3.00	3	4.00	4	4.00	4
1	4.00	4.00	4.00	4.00	4.00	4	4.00	4	4.00	4	4.00	4
1	3.00	4.00	4.00	3.00	3.00	3	4.00	3	3.00	3	2.00	2
1	4.00	4.00	4.00	4.00	3.00	3	4.00	4	4.00	4	3.00	3
1	2.00	2.00	2.00	2.00	3.00	3	2.00	2	4.00	4	3.00	3
0	5.00	5.00	5.00	5.00	5.00	5	5.00	5	5.00	5	5.00	5
1	3.00	3.00	3.00	3.00	4.00	3	4.00	3	3.00	4	3.00	4
1	4.00	3.00	4.00	3.00	4.00	3	4.00	3	4.00	3	4.00	3
1	2.00	2.00	2.00	2.00	2.00	2	2.00	2	3.00	3	3.00	3
1	4.00	3.00	4.00	3.00	4.00	3	4.00	3	4.00	4	4.00	4
1	5.00	5.00	5.00	5.00	5.00	5	5.00	5	5.00	5	5.00	5
1	4.00	4.00	4.00	4.00	4.00	4	4.00	4	3.00	3	4.00	4
1	4.00	3.00	4.00	3.00	3.00	3	3.00	3	4.00	3	4.00	3
1	4.00	4.00	4.00	4.00	4.00	4	4.00	4	4.00	4	3.00	3
1	4.00	4.00	5.00	5.00	5.00	5	4.00	4	4.00	4	3.00	3
1	4.00	4.00	4.00	4.00	4.00	4	4.00	4	4.00	4	4.00	4
1	1.00	5.00	1.00	5.00	1.00	5	1.00	5	3.00	5	3.00	5
1	2.00	4.00	3.00	5.00	2.00	5	2.00	5	2.00	5	3.00	5
1	2.00	2.00	2.00	2.00	2.00	2	2.00	2	2.00	3	3.00	3
0	4.00	4.00	4.00	4.00	4.00	3	3.00	3	5.00	3	3.00	3
0	4.00	5.00	4.00	4.00	4.00	3	3.00	3	4.00	4	3.00	3
1	5.00	5.00	5.00	5.00	5.00	5	5.00	5	5.00	5	5.00	5
1	4.00	4.00	4.00	4.00	4.00	4	3.00	3	4.00	4	4.00	4
1	2.00	2.00	2.00	2.00	2.00	3	2.00	2	3.00	3	4.00	4
1	5.00	5.00	5.00	5.00	5.00	5	5.00	5	5.00	5	5.00	5
1	4.00	4.00	3.00	3.00	4.00	4	3.00	3	4.00	4	3.00	3
0	3.00	3.00	4.00	4.00	3.00	3	3.00	3	5.00	5	5.00	5
1	4.00	4.00	4.00	4.00	4.00	4	4.00	4	5.00	5	4.00	4
1	1.00	1.00	2.00	2.00	2.00	2	2.00	2	2.00	2	3.00	3

WriflxR	WriflxL	WriextR	WriextL	HandgrpR	HandgrpL	HipflxR	HipflxL	HipextR	HipextL	KneeflxR	KneeflxL	KneeextR
5.00	5	4.00	4	1.00	1	4.00	4	5	5.00	4.00	4	5.00
4.00	2	4.00	2	1.00	1	4.00	2	3	2.00	3.00	3	4.00
4.00	5	4.00	5	1.00	1	4.00	5	4	5.00	4.00	5	4.00
3.00	3	4.00	3	1.00	1	5.00	5	5	5.00	4.00	4	5.00
5.00	5	5.00	5	1.00	1	4.00	5	4	5.00	3.00	5	4.00
4.00	4	4.00	4	1.00	1	5.00	5	5	5.00	5.00	5	5.00
4.00	4	4.00	4	1.00	1	4.00	4	4	4.00	4.00	4	4.00
2.00	3	2.00	2	1.00	1	3.00	4	4	3.00	3.00	3	3.00
4.00	4	3.00	3	1.00	1	4.00	4	4	4.00	4.00	4	4.00
3.00	3	1.00	1	1.00	1	4.00	4	4	4.00	4.00	4	4.00
5.00	5	5.00	5	1.00	1	5.00	5	5	5.00	5.00	5	5.00
3.00	2	2.00	2	1.00	1	4.00	4	4	4.00	5.00	5	5.00
3.00	2	3.00	2	1.00	1	4.00	4	4	4.00	4.00	4	4.00
2.00	2	2.00	2	1.00	1	4.00	4	4	4.00	4.00	4	3.00
5.00	3	4.00	4	0.00	1	3.00	3	3	3.00	4.00	4	4.00
4.00	4	4.00	4	1.00	1	5.00	5	5	5.00	5.00	5	5.00
4.00	4	4.00	4	1.00	1	5.00	5	5	5.00	5.00	5	5.00
4.00	3	4.00	3	1.00	1	3.00	4	3	4.00	3.00	4	3.00
4.00	4	3.00	3	1.00	1	4.00	4	4	4.00	4.00	4	4.00
4.00	4	3.00	3	1.00	1	4.00	4	4	4.00	3.00	3	4.00
4.00	4	4.00	4	0.00	0	5.00	5	5	5.00	5.00	5	5.00
2.00	4	2.00	4	1.00	0	5.00	5	5	5.00	5.00	5	5.00
3.00	5	2.00	5	1.00	0	5.00	5	5	5.00	5.00	5	5.00
3.00	3	2.00	2	1.00	1	2.00	3	2	3.00	3.00	3	3.00
3.00	3	2.00	2	1.00	1	4.00	4	2	2.00	4.00	4	4.00
4.00	3	3.00	3	1.00	1	5.00	5	4	4.00	4.00	4	5.00
5.00	5	5.00	5	0.00	0	4.00	4	4	4.00	4.00	4	4.00
4.00	4	4.00	4	1.00	1	4.00	4	4	4.00	3.00	3	4.00
4.00	4	3.00	3	1.00	1	2.00	1	2	2.00	2.00	2	3.00
5.00	5	5.00	5	0.00	0	5.00	5	5	5.00	5.00	5	5.00
3.00	3	2.00	2	1.00	1	3.00	2	4	3.00	3.00	3	4.00
5.00	5	5.00	5	0.00	0	3.00	3	4	4.00	4.00	4	4.00
4.00	4	3.00	4	1.00	1	4.00	4	4	4.00	4.00	4	4.00
3.00	3	1.00	1	1.00	1	4.00	3	3	3.00	2.00	2	3.00

KneeextL	DorsR	DorsL	PlflxR	PlflxL	DTRs	PlantarsR	PlantarsL	Supabd	FascicsH	FascicsE	Sensory	cerebellar
5	4.00	4	4.00	4	1	1	1	0	1.00	2.00	0	0
4	2.00	2	3.00	2	1	0	0	0	1.00	4.00	0	0
5	4.00	5	4.00	4	1	0	0	0	0.00	2.00	0	0
5	4.00	4	4.00	4	1	1	1	0	0.00	4.00	0	0
5	3.00	5	4.00	5	1	0	0	0	1.00	4.00	0	0
5	5.00	5	5.00	5	1	0	0	0	1.00	4.00	0	0
4	4.00	4	4.00	4	1	1	1	0	0.00	4.00	0	0
3	3.00	3	3.00	3	1	1	1	0	0.00	2.00	0	0
4	4.00	4	4.00	4	1	0	1	0	0.00	4.00	0	0
4	4.00	4	4.00	4	1	0	0	1	1.00	4.00	1	0
5	5.00	5	5.00	5	1	1	1	0	0.00	2.00	0	0
5	4.00	4	4.00	4	1	0	0	0	0.00	2.00	0	0
4	4.00	4	4.00	4	1	1	1	0	1.00	4.00	0	0
3	1.00	1	4.00	4	1	1	1	1	1.00	4.00	0	0
4	4.00	4	4.00	4	1	1	1	0	1.00	4.00	0	0
5	5.00	5	5.00	5	1	0	0	0	0.00	2.00	0	0
5	5.00	5	5.00	5	0	0	0	0	0.00	2.00	0	0
4	2.00	2	2.00	2	1	0	0	0	1.00	4.00	0	0
4	3.00	3	3.00	3	1	1	1	0	1.00	4.00	0	0
4	1.00	2	3.00	4	1	0	0	0	1.00	4.00	0	0
5	55.00	5	5.00	5	1	1	1	0	0.00	2.00	0	0
5	5.00	5	5.00	5	1	0	0	0	1.00	4.00	0	0
5	3.00	4	3.00	3	1	0	0	0	1.00	4.00	0	0
3	1.00	2	2.00	3	1	1	1	0	1.00	1.00	0	0
4	2.00	2	3.00	3	1	0	0	0	1.00	4.00	0	0
5	4.00	4	3.00	3	1	0	0	0	0.00	4.00	0	0
4	2.00	4	3.00	3	1	0	0	0	0.00	3.00	0	0
4	4.00	4	4.00	4	1	0	0	0	1.00	2.00	0	0
3	1.00	0	2.00	2	1	0	0	1	1.00	4.00	0	0
5	5.00	5	5.00	5	1	0	0	0	0.00	2.00	0	0
4	2.00	2	3.00	3	1	0	0	0	1.00	4.00	0	0
4	4.00	4	4.00	4	1	1	1	0	0.00	3.00	0	0
4	4.00	2	4.00	3	1	0	0	0	0.00	2.00	0	0
3	2.00	2	4.00	4	1	1	1	1	1.00	4.00	0	0

Romberg	Gait	rmcmp	rmcmprox	lmcmp	lmcmprox	rpcmp	rpcmprox	lpcmp	lpcmprox	rmdl	lmdl	rpdl
0	2	5.80	4.50	6.00	4.50	3.60	3.60	2.10	1.20	5.20	4.60	4.90
0	1	10.60	9.50	7.50	6.30	6.80	5.60	3.40	2.80	3.80	3.50	3.20
0	0	9.80	7.30	14.30	13.00	7.60	5.40	9.60	8.40	3.50	3.10	3.80
0	2	2.50	2.00	3.30	2.90	7.20	6.30	5.40	4.30	3.20	3.50	3.20
0	2	16.80	13.00	15.00	11.00	1.40	1.20	6.40	5.80	2.90	3.10	4.70
0	0	9.40	8.00	10.10	8.60	0.00	0.00	2.20	1.90	3.60	3.90	0.00
0	0	1.90	1.50	7.80	5.10	8.40	7.60	7.70	6.00	3.60	3.80	3.00
0	1	10.00	8.90	10.00	9.20	2.20	2.20	3.50	1.90	3.70	3.60	3.10
0	2	8.10	7.10	8.30	8.40	9.30	8.80	9.20	8.00	3.30	3.10	4.60
0	2	0.50	0.50	4.70	4.60	2.60	2.30	13.80	10.90	4.60	4.10	3.80
0	0	3.20	2.30	3.20	2.50	6.40	3.00	4.90	3.10	3.70	4.20	3.80
0	2	6.50	4.90	1.70	1.30	8.50	7.20	6.40	4.80	3.50	3.70	3.30
0	2	0.10	0.10	0.00	0.00	0.40	0.40	2.40	2.40	4.60	0.00	4.70
0	1	2.00	1.90	0.20	0.20	2.90	2.60	0.80	0.60	4.30	5.30	4.40
0	2	13.70	11.30	11.50	8.00	9.30	6.60	1.90	1.40	3.20	3.30	2.80
0	2	7.40	5.70	4.40	3.90	7.60	7.00	7.70	5.20	4.00	4.80	3.70
0	0	7.80	5.50	10.70	8.10	6.20	4.50	5.70	4.80	4.00	3.90	4.30
0	1	0.00	0.00	0.40	0.30	3.80	2.50	5.60	4.40	5.50	2.90	3.30
0	1	5.60	4.00	8.00	7.60	7.00	6.50	4.90	4.60	4.40	3.90	4.30
0	1	1.80	1.20	2.30	1.30	0.00	0.00	1.40	1.40	2.90	4.00	0.00
0	0	11.20	8.90	12.90	10.90	12.20	10.00	9.00	6.80	3.00	3.20	2.70
0	2	0.50	0.40	6.30	4.90	6.90	6.00	12.20	10.00	5.70	3.20	3.90
0	2	1.80	1.10	8.30	7.30	8.80	6.90	7.50	5.60	3.30	3.40	3.70
0	1	3.50	3.50	5.70	5.30	0.90	0.90	0.20	0.20	4.20	3.00	4.30
0	1	0.20	0.20	1.90	1.10	1.30	1.10	2.20	2.20	3.30	4.60	4.60
0	0	6.40	4.30	5.60	4.80	5.30	3.90	4.40	3.30	3.20	3.00	4.20
0	2	15.50	12.40	21.50	20.70	0.30	0.30	2.30	1.90	2.80	2.70	4.40
0	2	13.90	12.90	15.10	14.00	6.70	6.00	6.00	5.50	3.20	3.10	2.60
0	1	2.90	2.10	3.40	2.70	0.00	0.00	0.00	0.00	5.60	4.40	0.00
0	0	14.00	11.50	12.20	12.20	12.80	10.30	10.40	8.50	2.80	3.70	3.20
0	1	0.10	0.10	0.30	0.30	4.40	3.80	0.00	0.00	6.50	5.30	0.00
0	2	6.60	5.00	4.80	4.20	12.80	10.80	12.00	9.20	4.80	4.00	4.20
0	2	1.30	0.90	6.20	5.00	9.00	8.10	4.50	3.80	5.00	4.00	3.40
0	1	0.00	0.00	0.00	0.00	0.70	0.70	3.00	3.00	0.00	0.00	5.20

lpdl	rmf	lmf	rpf	lpf	rmcv	lmcv	rpcv	lpcv	rmsnp	lmsnp	rsnp	lssnp
5.30	27.80	28.20	46.90	43.00	46.00	49.00	41.00	54.00	96.00	87.00	34.00	22.00
4.80	24.30	23.90	41.90	43.10	55.00	57.00	44.00	40.00	31.00	28.00	36.00	37.00
3.50	28.90	24.90	41.80	48.40	53.00	56.00	54.00	55.00	46.00	35.00	45.00	41.00
3.30	27.90	25.40	46.60	43.40	57.00	59.00	51.00	51.00	9.00	70.00	22.00	21.00
4.30	25.10	24.60	51.50	50.60	56.00	62.00	47.00	45.00	40.00	46.00	23.00	27.00
4.80	29.70	30.40	0.00	51.50	55.00	50.00	0.00	42.00	32.00	42.00	22.00	20.00
3.40	29.40	29.70	41.70	41.70	57.00	60.00	47.00	53.00	46.00	50.00	64.00	61.00
3.30	25.80	25.40	42.40	47.30	63.00	54.00	58.00	52.00	25.00	20.00	16.00	20.00
5.10	27.80	25.20	46.60	46.80	61.00	58.00	43.00	49.00	28.00	24.00	33.00	29.00
3.30	0.00	29.10	56.50	52.60	76.00	55.00	58.00	47.00	67.00	70.00	58.00	63.00
3.10	22.30	31.30	40.30	40.10	44.00	48.00	50.00	51.00	35.00	21.00	24.00	28.00
3.30	21.10	25.60	48.00	43.90	59.00	60.00	51.00	53.00	49.00	52.00	37.00	32.00
4.70	0.00	0.00	0.00	46.00	38.00	0.00	41.00	49.00	41.00	35.00	22.00	27.00
5.10	33.00	0.00	55.70	52.20	40.00	48.00	45.00	44.00	30.00	25.00	27.00	23.00
4.40	23.30	26.10	41.40	42.70	65.00	52.00	69.00	64.00	90.00	84.00	50.00	59.00
4.20	28.30	27.70	44.70	45.30	55.00	62.00	52.00	54.00	35.00	53.00	26.00	24.00
4.70	29.80	28.00	54.70	52.70	56.00	53.00	48.00	51.00	21.00	20.00	19.00	18.00
3.60	0.00	0.00	43.40	51.90	0.00	64.00	58.00	58.00	32.00	29.00	15.00	10.00
4.40	31.70	21.60	41.70	40.90	79.00	67.00	58.00	64.00	27.00	33.00	31.00	32.00
4.80	26.60	26.50	0.00	0.00	50.00	68.00	0.00	43.00	66.00	44.00	30.00	21.00
2.70	24.70	24.20	38.50	38.90	45.00	58.00	45.00	49.00	88.00	75.00	52.00	77.00
3.50	32.90	27.10	46.20	43.90	51.00	57.00	47.00	45.00	42.00	46.00	21.00	24.00
3.70	0.00	29.30	48.20	49.30	51.00	49.00	49.00	46.00	41.00	35.00	26.00	20.00
4.80	30.90	31.40	0.00	0.00	51.00	48.00	41.00	30.00	19.00	27.00	14.00	13.00
4.20	0.00	0.00	49.60	51.30	70.00	53.00	47.00	46.00	36.00	37.00	27.00	22.00
4.10	29.00	31.80	51.70	52.00	57.00	57.00	45.00	45.00	23.00	22.00	10.00	6.00
3.10	29.80	23.90	52.90	55.00	59.00	58.00	34.00	40.00	36.00	46.00	50.00	46.00
2.90	23.90	24.50	43.50	44.10	58.00	62.00	49.00	53.00	22.00	25.00	28.00	23.00
0.00	33.70	33.90	0.00	0.00	48.00	54.00	0.00	0.00	23.00	24.00	20.00	17.00
3.60	25.50	24.50	44.50	46.30	55.00	68.00	45.00	49.00	35.00	33.00	24.00	31.00
5.00	0.00	0.00	51.10	0.00	47.00	44.00	46.00	0.00	54.00	57.00	23.00	36.00
4.40	38.30	30.00	44.50	49.60	51.00	57.00	51.00	51.00	96.00	43.00	31.00	59.00
3.80	31.00	28.00	46.00	49.00	60.00	57.00	48.00	48.00	41.00	37.00	27.00	58.00
2.80	0.00	0.00	0.00	49.30	0.00	0.00	56.00	48.00	20.00	30.00	19.00	23.00

rucmp	rucmprox	lucmp	lucmprox	rudl	ludl	ruf	luf	rucv	lucv	rusnp	lusnp	PhrenicL
8.90	5.70	9.90	5.60	3.60	3.80	27.40	27.80	54.00	53.00	65.00	73.00	7.20
8.30	6.00	6.10	6.10	2.50	2.70	24.10	24.00	51.00	77.00	28.00	30.00	0.00
4.50	2.90	18.40	16.70	3.50	2.70	30.50	26.30	59.00	62.00	31.00	22.00	0.00
4.00	2.40	2.40	1.90	2.60	2.90	26.50	27.80	58.00	52.00	23.00	35.00	7.20
14.80	12.10	11.10	10.50	2.10	2.10	26.50	26.80	65.00	64.00	35.00	30.00	8.20
10.60	9.70	8.50	6.40	2.80	3.50	28.80	28.20	56.00	57.00	25.00	25.00	7.80
4.80	2.50	5.70	3.50	2.70	2.90	27.40	31.50	63.00	63.00	25.00	36.00	0.00
9.50	8.70	10.30	9.30	3.00	2.10	26.40	23.90	78.00	84.00	20.00	24.00	0.00
6.50	5.90	8.10	6.30	2.80	2.70	27.60	26.70	64.00	58.00	32.00	34.00	0.00
2.50	2.40	3.10	2.10	2.60	3.50	31.40	30.20	50.00	57.00	32.00	27.00	4.40
10.80	7.20	9.00	7.00	2.90	3.80	25.40	25.90	71.00	60.00	22.00	31.00	0.00
1.60	1.40	1.60	1.40	3.40	3.50	29.40	29.40	63.00	59.00	31.00	25.00	0.00
9.20	8.80	0.40	0.40	2.90	5.40	29.40	0.00	60.00	47.00	63.00	67.00	0.00
1.30	1.10	1.60	1.40	4.10	4.50	29.80	30.20	55.00	55.00	70.00	67.00	0.00
15.10	12.00	8.80	7.10	2.20	2.90	22.40	27.50	71.00	53.00	40.00	38.00	0.00
10.30	8.40	7.10	5.40	2.90	2.80	27.50	26.20	63.00	59.00	38.00	32.00	0.00
12.50	11.20	10.80	9.80	3.00	3.50	30.30	30.30	55.00	60.00	19.00	17.00	8.40
3.10	2.50	4.30	2.10	2.90	2.80	30.20	0.00	61.00	58.00	27.00	18.00	7.10
1.20	1.20	0.80	0.70	3.10	3.80	0.00	0.00	62.00	63.00	22.00	21.00	0.00
8.30	7.10	5.30	3.90	2.80	3.00	29.10	28.30	64.00	60.00	36.00	49.00	7.00
12.00	10.40	12.00	8.50	2.80	2.70	24.10	24.70	67.00	60.00	41.00	45.00	7.00
0.00	0.00	7.40	6.80	0.00	2.70	0.00	27.20	0.00	65.00	29.00	25.00	7.20
3.90	3.10	13.60	11.90	3.00	2.90	33.00	31.00	55.00	63.00	21.00	21.00	0.00
3.60	2.90	8.90	7.50	3.20	3.10	31.50	29.30	48.00	58.00	14.00	24.00	9.00
0.80	0.80	3.00	1.60	3.20	2.70	0.00	0.00	77.00	60.00	25.00	42.00	0.00
9.50	8.70	4.70	3.50	3.10	3.20	29.50	32.40	56.00	62.00	15.00	14.00	0.00
11.50	8.90	12.30	10.10	2.50	2.40	24.00	26.00	57.00	63.00	65.00	58.00	0.00
14.00	13.00	12.70	10.70	2.10	2.20	24.50	23.00	63.00	72.00	25.00	27.00	0.00
4.40	3.10	6.80	4.70	3.90	3.70	35.60	31.90	40.00	42.00	18.00	21.00	0.00
13.30	11.10	13.70	11.80	2.60	2.60	27.30	28.50	63.00	69.00	23.00	29.00	0.00
2.70	1.60	5.40	3.70	4.70	3.60	0.00	34.00	42.00	52.00	23.00	25.00	0.00
4.90	2.90	6.10	4.60	3.30	3.30	28.80	37.70	60.00	60.00	42.00	40.00	0.00
4.90	3.70	7.00	5.60	2.90	2.60	30.00	46.00	63.00	59.00	27.00	27.00	0.00
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	21.00	25.00	8.70

PhrenicA	Proxconduc	Condbloc	AcDenerBulb	AcDenerCer	AcDenerTho	AcDenerLS	ChrDenerBulb	ChrDenerCer	ChrDenerTho	ChrDenerLS	Elesco	Awaji
4.30	0.00	3.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	0.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.80	0.00	3.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.70	1.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
2.90	0.00	3.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	0.00	1.00	1.00	0.00	0.00	0.00	1.00	0.00	1.00	1.00	1.00
0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	1.00	0.00	1.00	2.00	1.00
0.00	0.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
2.40	0.00	0.00	1.00	1.00	0.00	1.00	1.00	1.00	0.00	1.00	0.00	0.00
0.00	1.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	0.00	1.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	1.00	0.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	2.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
1.10	1.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.60	1.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	0.00	1.00	1.00	1.00	0.00	0.00	1.00	0.00	1.00	0.00	0.00
0.70	0.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
1.20	0.00	0.00	1.00	1.00	0.00	0.00	0.00	1.00	0.00	1.00	1.00	0.00
0.50	0.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
1.00	0.00	0.00	0.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	1.00	0.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	2.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	1.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	0.00	1.00	1.00	1.00
0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	1.00	0.00
0.00	0.00	3.00	0.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00	1.00	0.00	1.00	1.00	0.00
0.00	0.00	3.00	0.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
0.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	0.00
1.80	0.00	2.00	1.00	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00

Spirometry	Barium	CSFC	CSFP	Immune	Toxscrn	PEG	MRI1	MRI2	PET	Therapy	Response	duration
1.00	1.00	1.00	2.00	2.00	2.00	0.00	1.00	3.00	0.00	2.00	2.00	12.00
1.00	2.00	1.00	1.00	1.00	0.00	2.00	1.00	2.00	1.00	1.00	1.00	12.00
1.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	2.00	0.00	2.00	2.00	24.00
1.00	0.00	1.00	1.00	1.00	1.00	0.00	1.00	3.00	2.00	2.00	1.00	15.00
0.00	0.00	1.00	1.00	1.00	0.00	0.00	1.00	2.00	1.00	0.00	1.00	6.00
3.00	2.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	48.00
0.00	0.00	1.00	1.00	0.00	2.00	0.00	1.00	1.00	0.00	1.00	1.00	8.00
1.00	1.00	0.00	0.00	1.00	0.00	0.00	1.00	2.00	2.00	2.00	1.00	24.00
4.00	1.00	1.00	1.00	1.00	0.00	0.00	1.00	3.00	2.00	1.00	1.00	12.00
1.00	3.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	0.00	2.00	1.00	24.00
4.00	1.00	1.00	1.00	1.00	0.00	0.00	1.00	1.00	2.00	1.00	2.00	12.00
4.00	1.00	1.00	1.00	1.00	0.00	0.00	1.00	1.00	0.00	1.00	1.00	24.00
4.00	1.00	1.00	2.00	1.00	1.00	0.00	1.00	1.00	0.00	1.00	1.00	60.00
1.00	1.00	1.00	1.00	1.00	0.00	0.00	1.00	3.00	1.00	2.00	1.00	12.00
0.00	0.00	1.00	1.00	1.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	6.00
0.00	1.00	1.00	1.00	1.00	0.00	0.00	1.00	1.00	0.00	1.00	1.00	12.00
0.00	1.00	1.00	2.00	1.00	0.00	0.00	1.00	1.00	2.00	2.00	1.00	12.00
3.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	3.00	0.00	1.00	2.00	8.00
1.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	3.00	0.00	2.00	1.00	36.00
0.00	0.00	1.00	1.00	1.00	0.00	0.00	1.00	1.00	0.00	2.00	1.00	24.00
1.00	3.00	1.00	1.00	1.00	0.00	0.00	1.00	1.00	0.00	2.00	1.00	9.00
1.00	1.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	0.00	2.00	2.00	36.00
0.00	0.00	1.00	2.00	1.00	0.00	0.00	1.00	1.00	1.00	2.00	1.00	14.00
1.00	0.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	0.00	1.00	1.00	18.00
1.00	3.00	1.00	2.00	1.00	1.00	0.00	1.00	3.00	1.00	2.00	2.00	16.00
1.00	3.00	1.00	1.00	1.00	1.00	0.00	1.00	2.00	2.00	2.00	1.00	36.00
0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	2.00	24.00
0.00	0.00	1.00	1.00	1.00	0.00	0.00	1.00	2.00	1.00	1.00	0.00	72.00
1.00	0.00	0.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	2.00	2.00	8.00
1.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00	1.00	4.00
1.00	0.00	1.00	2.00	1.00	1.00	0.00	1.00	1.00	0.00	2.00	2.00	18.00
0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	3.00	0.00	2.00	1.00	6.00
1.00	0.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	2.00	1.00	15.00
3.00	2.00	0.00	0.00	2.00	1.00	1.00	1.00	1.00	0.00	2.00	0.00	84.00

Onset	Progression1	Progression2	ALSFRS	Outcome	Followup1	Followup2	CognitionP	CognitionN	CognitionA	CognitionACE	CognitionF	RTCorFA
2.00	1.00	2.00	32.00	0.00	3.00	0.00	1.00	1.00	2.00	1.00	2.00	0.53
1.00	0.00	2.00	35.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.47
0.00	1.00	2.00	29.00	0.00	0.00	0.00	1.00	1.00	2.00	1.00	1.00	0.50
1.00	0.00	3.00	38.00	0.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	0.56
2.00	3.00	1.00	32.00	0.00	0.00	0.00	1.00	1.00	2.00	2.00	3.00	0.51
0.00	2.00	3.00	29.00	0.00	3.00	3.00	1.00	1.00	2.00	2.00	3.00	0.50
1.00	0.00	2.00	40.00	0.00	3.00	0.00	1.00	2.00	2.00	1.00	1.00	0.59
1.00	0.00	2.00	40.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.53
1.00	0.00	2.00	43.00	0.00	0.00	3.00	1.00	2.00	2.00	2.00	1.00	0.53
1.00	0.00	1.00	33.00	0.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	0.56
0.00	2.00	2.00	44.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.51
1.00	0.00	3.00	42.00	0.00	0.00	0.00	1.00	1.00	2.00	2.00	1.00	0.45
1.00	0.00	3.00	36.00	0.00	0.00	0.00	1.00	1.00	2.00	1.00	1.00	0.43
1.00	0.00	1.00	33.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.49
1.00	0.00	2.00	42.00	0.00	3.00	0.00	1.00	1.00	1.00	1.00	1.00	0.60
0.00	2.00	2.00	42.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.51
0.00	2.00	2.00	42.00	0.00	0.00	0.00	1.00	1.00	2.00	2.00	1.00	0.53
1.00	0.00	2.00	33.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.48
2.00	1.00	1.00	29.00	0.00	3.00	3.00	1.00	2.00	2.00	2.00	1.00	0.39
2.00	1.00	1.00	34.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.41
0.00	2.00	2.00	38.00	0.00	3.00	0.00	1.00	1.00	1.00	1.00	1.00	0.52
1.00	0.00	3.00	36.00	0.00	0.00	0.00	1.00	1.00	2.00	2.00	1.00	0.48
1.00	0.00	2.00	42.00	0.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	0.51
2.00	1.00	2.00	35.00	0.00	2.00	3.00	1.00	1.00	2.00	1.00	1.00	0.45
2.00	1.00	1.00	28.00	0.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	0.50
1.00	0.00	3.00	44.00	0.00	3.00	0.00	2.00	2.00	2.00	2.00	4.00	0.52
2.00	1.00	2.00	44.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.47
0.00	4.00	3.00	42.00	0.00	0.00	2.00	1.00	1.00	1.00	1.00	1.00	0.37
2.00	1.00	1.00	29.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.51
0.00	2.00	2.00	37.00	0.00	2.00	0.00	1.00	1.00	2.00	2.00	1.00	0.51
2.00	1.00	1.00	29.00	0.00	2.00	3.00	1.00	1.00	1.00	1.00	1.00	0.48
2.00	1.00	1.00	34.00	0.00	2.00	3.00	1.00	1.00	2.00	1.00	1.00	0.50
2.00	1.00	2.00	35.00	0.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	0.43
1.00	0.00	1.00	14.00	0.00	2.00	3.00	1.00	1.00	2.00	1.00	1.00	0.56

LTCorFA	RTPLICFA	LTPLICFA	RPenFA	LPenFA	RPyrFA	LPyrFA	RTCorMD	LTCorMD	RTPLICMD	LTPLICMD	RPenMD	LPenMD
0.57	0.69	0.65	0.71	0.77	0.55	0.54						
0.52	0.72	0.58	0.66	0.68	0.44	0.44	1.06	1.10	0.81	0.78	1.05	0.82
0.51	0.56	0.57	0.65	0.66	0.50	0.38	0.86	0.77	0.89	0.86	0.90	1.01
0.55	0.56	0.59	0.63	0.61	0.47	0.45	0.83	0.86	0.94	0.82	0.81	1.00
0.31	0.70	0.65	0.62	0.73	0.54	0.54						
0.60	0.64	0.67	0.57	0.82	0.48	0.54	0.98	0.93	0.81	0.78	0.88	0.96
0.49	0.62	0.64	0.67	0.75	0.49	0.46	0.88	0.84	0.95	0.84	0.83	0.92
0.49	0.62	0.58	0.53	0.77	0.52	0.51	0.83	0.89	0.92	0.79	0.97	0.85
0.51	0.58	0.59	0.61	0.62	0.41	0.42	1.00	0.83	0.96	0.83	1.00	0.93
0.54	0.58	0.62	0.68	0.74	0.53	0.51	0.94	0.90	0.85	0.89	0.88	0.82
0.47	0.56	0.66	0.65	0.64	0.48	0.49	0.85	0.94	0.87	1.02	0.85	1.16
0.47	0.58	0.63	0.63	0.72	0.43	0.51	1.02	1.05	1.01	1.00	1.05	0.95
0.51	0.65	0.67	0.66	0.62	0.45	0.46	0.91	0.89	1.01	1.06	0.85	0.99
0.47	0.63	0.63	0.65	0.74	0.47	0.49	0.80	0.81	1.09	1.00	0.82	0.82
0.54	0.75	0.68	0.67	0.74	0.50	0.42	0.96	0.77	0.94	0.86	0.92	0.92
0.47	0.58	0.61	0.61	0.68	0.49	0.42	0.91	0.91	1.05	1.01	0.86	0.86
0.57	0.69	0.65	0.69	0.75	0.50	0.50	0.90	0.76	0.90	0.84	0.84	0.94
0.46	0.64	0.66	0.62	0.62	0.55	0.51	0.86	0.90	0.88	0.78	0.89	0.90
0.31	0.62	0.58	0.63	0.60	0.48	0.44						
0.38	0.62	0.62	0.68	0.73	0.55	0.58						
0.36	0.63	0.65	0.60	0.68	0.48	0.56						
0.56	0.61	0.63	0.63	0.73	0.45	0.42	0.79	0.97	0.87	0.87	1.03	0.86
0.55	0.69	0.65	0.71	0.67	0.49	0.52						
0.53	0.67	0.62	0.66	0.73	0.48	0.51	0.95	0.85	0.84	1.00	0.86	0.72
0.52	0.68	0.62	0.67	0.66	0.50	0.54	0.88	0.92	0.98	0.92	0.86	0.92
0.49	0.67	0.65	0.65	0.67	0.43	0.52	0.86	0.89	0.86	0.87	0.85	0.83
0.40	0.68	0.71	0.71	0.72	0.63	0.56						
0.33	0.68	0.63	0.58	0.63	0.51	0.53						
0.50	0.65	0.67	0.70	0.66	0.55	0.49	0.94	0.84	0.79	0.96	1.01	0.82
0.46	0.67	0.65	0.73	0.77	0.48	0.49						
0.55	0.67	0.68	0.75	0.73	0.59	0.58						
0.55	0.51	0.62	0.69	0.69	0.41	0.47						
0.39	0.72	0.63	0.75	0.72	0.62	0.63						
0.58	0.68	0.65	0.62	0.75	0.39	0.48	0.84	0.83	0.91	0.87	0.86	0.95

RPyrMD	LPyrMD
0.78	0.82
0.98	1.01
0.89	0.89
0.81	0.88
0.95	0.74
0.86	0.93
0.90	0.90
1.00	0.97
0.98	0.93
0.68	0.94
1.10	0.86
1.03	0.99
1.08	0.83
1.10	1.00
1.00	0.97
0.93	0.90
1.03	0.76
0.87	0.72
1.03	0.84
0.70	0.93
0.75	0.74
1.10	0.93